Report of the sixth international workshop on X chromosome mapping 1995

Prepared by D.L. Nelson, A. Ballabio, F. Cremers, A.P. Monaco, and D. Schlessinger;

with assistance from the X chromosome community and in particular: D. Bentley, Y. Boyd, S. Brown, R.A. Cottingham and G. Herman

The momentum generated by the X chromosome community has continued to move the map forward and to exploit it increasingly for functional, disease gene, and comparative evolutionary analyses. Based on the progress in the last year, the coming year should see the assembly of YAC coverage in the remaining uncovered sections of the chromosome; the integration of the genetic and physical maps; and the approach to STS formatting with inter- marker distances generally no greater than 100 kb. In addition to developing summaries of the state of regions of the map, as presented below, the advanced degree of map completion fostered a notable shift in the dynamics of interaction of groups. As the map approaches closure, for example, groups looking for a particular disease gene all have adequate cloned materials to advance the searches for candidate genes. For the community as a whole, extensive discussions dealt with the way in which clones and STSs could be provided to everyone, what types of clones might be best to supplement current YAC-based maps; how to approach long-range sequencing; and how future meetings might be structured.

YAC contigs with an average clone depth of at least four-fold coverage, sufficient to sustain gene finding and the organization of long-range sequencing, now span more than 90% of the chromosome. The remaining gaps are delimited, primarily in Xp11.3 and Xq13, and are already represented in partially organized contigs. Many regions are still covered only by single clones; but in general, these should be supplementable by additional screening with STSs, since the formatting of contigs is also progressing. With map resolution defined as the average distance between ordered markers, the chromosome is completely covered at an average inter-STS distance of 500 kb; 93% covered at 200 kb; and over 60% covered at 100 kb.

The consistent progress led to three discussions in which consensus views were developed on the logistics to provide materials to the community; on possible approaches to the sequencing of the chromosome; and on the possible future structure of X chromosome workshops.

Regarding the provision of materials, STSs are increasingly found in GDB, and a subset of 2100 robust STSs that cover nearly all of the chromosome are accessible through the World Wide Web (WWW) server at the St. Louis Genome Center. The Workshop participants agreed to construct jointly a collection of verified X-specific YACs from currently widely-used libraries. These would tentatively include 6,000 from the St. Louis Genome Center (already deposited in ATCC), about 1,000 from the Baylor Center, about 2,000 from the Sanger Centre, about 2,000 from the ICRF collection, and X-specific YACs from CEPH as well as Leiden and other Centers. Duplications would be evident, since all of these collections are currently described on WWW pages and (at least for some collections) in GDB. All the participating groups will provide the clones to the Berlin Resources Center, directed by H. Lehrach, in the next months. The Berlin Center will replicate complete sets of about 100–120 96-well microtiter plates for 12 groups who requested complete sets. Most of those groups would undertake to provide sets to additional groups; and the ATCC could provide an alternative source of clones or sets of clones at low cost.

These materials will provide a unified set of reagents for the X community. As for the handling of data in the future, representations from the GDB provided one way to integrate future materials from Web sites and the literature into a single source. Alternatives would be to enter all data into additional databases (such as the Reference Library DataBase, which has served a partial role of this type and was offered as an option by H. Lehrach), or in a mixture of Web site and GDB offerings.

The current YAC holdings are adequate to support the movement toward gene-finding and sequencing. However, coverage of regions of the chromosome with bacterial clones, including cosmids, BACs, etc. is being actively pursued at

several sites as a source of sequencing substrates, and suggesting a Consortium approach to massive sequencing across the X (see discussion of Sequencing Prospects below).

The World Wide Web (Web) protocol on Internet has fostered a ubiquitous, inexpensive system for disseminating information. This has now reached the X community in the form of the X Chromosome Virtual Workshop (Abst I2). This Web service presents all of the abstracts from the workshop and a list of participants including email addresses. Since the meeting several people have submitted their posters which have been linked to the associated abstract. This allows people who were unable to attend the meeting to still be able to view the posters, and to directly contact the authors for further discussion since the email addresses of participants are linked to the abstract author list.

In addition the X Chromosome Virtual Workshop has a variety of links to X chromosome related services currently available including access to genetic and physical maps from around the community. Also the Virtual Workshop has an online discussion area organized by map region where people can comment on the map and abstracts in that region. The X Chromosome Virtual Workshop can be accessed using URL: <http://gc.bcm.tmc.edu:8088/chrx/home.html>.

An X Chromosome Workshop email list service has also been established which will send a message to all participants at <chrx@listserv.bcm.tmc.edu>.

Many community informatics resources are now available via the Web making them easier to browse. These include the Genome Data Base (http://gdbwww.gdb.org/), and the sequence databases:

GSDB (http://www.ncgr.org/gsdb/gsdb.html),
NCBI (http://www.ncbi.nlm.nih.gov/), and
EMBL
(http://www.ebi.ac.uk/ebi_docs/embl_db/ebi/topembl.html).

Also each of these sites has information on how to submit data and obtain further help.

GDB currently can store all genetic and physical mapping data. Future versions of the GDB software will significantly enhance the display and editing of maps. This will include a tool for submitting, viewing and editing graphical maps. Also SIGMA will be supported for presenting community consensus maps.

Network news groups bionet.genome.chromosomes and bionet.molbio.gdb may be of interest to those in the X community. Methods for accessing these are posted on group bionet.announce monthly. These are also accessible with Web browsers.

Those interested in accessing any of these sources of information should contact their local computing service personnel for advice and assistance on setting up a Web browser. Also there are a large number of popular books on accessing the Web which can be found at any bookstore.

Finally, the community agreed tentatively to work toward a Consortium map to be as definitive as possible, assembled in time for the next X workshop in Cambridge, England (hosted by D. Bentley), tentatively in June, 1996. On that basis, it was considered that future meetings might evolve toward the consideration of a mix of studies of sequencing and sex chromosome biology.

Region-specific reports:

pter→p21.3

Physical/genetic map

This section of the map spans from pter to DXS28 and measures approximately 35–40 Mb. There has been considerable activity in building/refining YAC contigs in this region of the X chromosome, most of which is now covered by overlapping YACs. The only two gaps remaining are located within the pseudoautosomal region (around CSF2RA and XE7)(DXYS155E) and are estimated to be less than 50 kb (abst. B15). These gaps were also present in previously described YAC collections and could not be filled with either YAC, cosmid, or phage clones.

An integrated physical and genetic map spanning the 35 Mb from the pseudoautosomal boundary (PABX) to DXS726, has been reported by Ferrero et al. (abst. B1 and Ferrero et al., in press). The map includes 85 breakpoints organized into a 54-interval deletion panel. Over 200 markers were ordered through the region, including 185 STSs (average spacing 1/190 kb), 18 genes, 10 disease genes, 37 STRs, and 11 reference genetic markers. Five hundred and eighty-five YAC clones from 5 different libraries were assembled in one uninterrupted contig organized into 183 occupied bins averaging 195 kb in size (abst. B1 and Ferrero et al., in press). Selected YAC clones from this map were amplified using a modified Alu-PCR technique favoring amplification of long fragments and hybridized to the flow-sorted Lawrence Livermore National Laboratories X chromosome specific cosmid library. Approximately 1,500 cosmid clones were identified and assigned to specific YACs (abst. B3).

Physical mapping efforts have been produced by several groups in regions surrounding specific disease genes. Herrel et al. reported 6 YAC contigs including 54 YAC clones and spanning the CDPX, STS, KAL and OA1 genes in the p22.3–p22.2 region. These contigs are associated with a detailed long-range restriction map pinpointing several CpG islands (Herrell et al., 1995). A 6-Mb contig including 70 overlapping YAC clones, which cover the interval between DXS16 and DXS1229 in the p22.2–p22.1 region, was reported by Alitalo et al. This contig has an STS density of approximately 1/100 kb and spans the genes for CALB3, GRPR, PIGA, GLRA2, PHKA2, XE59, and DXS69E (Alitalo et al.). Additional YAC contigs were assembled around the CDPX (Wang et al.), CLS (abst. B2, B5, B6, B7), KFSD (abst. B2, B6), RS (abst. B4, B5, B6), and the HYP genes (abst. B2, B6, B9).

New genes

A cluster of three genes, displaying homology with all previously identified members of the sulfatase gene family, has been isolated from the Xp22.33 region (Franco et al., 1995) (abst. B13). These genes, named arylsulfatase D, E, and F (ARSD, ARSE, and ARSF) are located within the X-linked recessive chondrodysplasia punctata (CDPX) critical region in the X-specific region, just proximal to the pseudoautosomal boundary (PABX). Full-length cDNAs were identified for the ARSD and ARSE genes, while recent data suggest that ARSF might be a truncated pseudogene. Both the ARSD and ARSE genes escape X inactivation and have a Y-linked homologue. Point mutations in the ARSE gene have been found in patients with CDPX. The ARSE gene encodes a novel heat-labile sulfatase that is inhibited by warfarin, suggesting that ARSE is involved in the typical bone and cartilage abnormalities found in both CDPX and warfarin embryopathy (Franco et al., 1995) (abst. B13).

A gene encoding a novel type of human protein kinase, PKX1, has been isolated from the Xp22.33 region (Klink et al. 1995) (abst. B14). PKX1 is located between ARSF and DXS7099. PKX1 protein product is related to the cAMP-dependent protein kinases and has striking homology to the DC2 protein kinase of *Drosophila melanogaster*. The gene is part of a family with at least an additional member located on the X chromosome and appears to be a site for chromosomal rearrangements. A Y-linked homologue was mapped to Yp (Klink et al., 1995) (abst. B14).

A gene homologous to the *Xenopus laevis* APX (Apical Protein Xenopus) gene has been identified from the ocular albinism type 1 critical region in Xp22.31 (Schiaffino et al., 1995). This gene, named APXL (APX-like), spans over 70% of the OA1 critical region. However, SSCP analysis and direct sequencing in OA1 patients did not reveal any functionally significant mutations, thus excluding a direct involvement of APXL in OA1. A truncated pseudogene homologous to the rat *Elf5* gene, a eukaryotic translation initiation factor, is located in intron 1 of the APXL gene (Schiaffino et al., 1995).

Further gene searches in the OA1 critical region have led to the identification of a novel gene which appears to be expressed exclusively in highly pigmented tissues, such as retinal pigment epithelium and melanoma (Bassi et al., 1995) (abst. B13). A direct involvement of this gene in OA1 has been demonstrated through the detection of several intragenic deletions and point mutations in OA1 patients. The OA1 gene encodes a protein containing several putative transmembrane domains and sharing no similarities with previously identified molecules (Bassi et al., 1995) (abst. B13).

Two previously identified genes, CD39 a late lymphocyte activation antigen, and ISPK1 (insulin sensitive protein kinase 1), initially mapped to the X chromosome using somatic cell hybrid panels (Voland et al., 1992 and Bjorbaek et al., 1995), have now been assigned to specific positions in Xp22. CD39 was mapped to the PAR, within YACs yWXD2565 and yWXD5167 and between loci DXYS15 and CSF2RA (abst. B12). RT-PCR experiments demonstrated that the CD39 gene is expressed by both the active and the inactive X and by the Y chromosome (abst. B12). ISPK1 was mapped to p22.13 between DXS3424 and DXS1229, within the CLS critical region (abst. B2).

New assignments/refined positions of disease loci

A new type of syndromic X-linked mental retardation has been assigned to Xp22.2–pter (abst. B11). This disorder has been observed in one family and is characterized by mental retardation and several congenital anomalies, including facial dysmorphisms, microphthalmos, sclerocornea, atrophy of the optic nerve, abnormal EEG, short stature, delayed bone maturation, renal abnormalities, cryptorchidism, clinodactily V, and transverse palmar creases. The disease locus appears to cosegregate with KAL, DXS278, and DXS16 in Xp22 (abst. B11).

The position of the retinoschisis locus (RS) has been significantly refined (abst. B4 and B6). Van de Vosse et al. mapped this locus between DXS418 and DXS999, a region which according to physical mapping data, measures approximately 600 kb (abst. B6). The same group has assigned the keratosis follicularis spinulosa decalvans (KFSD) locus to a 1 Mb region between DXS257/DXS7161 and DXS1226 (abst. B6).

The critical region for Coffin-Lowry syndrome (CLS) has also been narrowed considerably (abst. B2, B5, B7). Bird et al. have reported data indicating a localization of CLS between DXS7161 and DXS365 (Bird et al., in press) (abst. B7), an interval measuring approximately 2.2 cM.

Significant progress has been made in the effort aimed at the identification of the X-linked dominant hypophosphatemic rickets (HYP) gene (abst. B7, B8). The critical region has now been narrowed to approximately 300 kb spanned by a single YAC clone and gene searches have been initiated in this region (abst. B8). Using a south/western binding assay, a putative vitamin D responsive element, which may be the product of the HYP gene, has been identified in this region. A major breakthrough has been the finding of a microdeletion in a patient with HYP. This microdeletion was identified by Southern blot analysis using a cosmid containing the putative vitamin D responsive element as a probe (abst. B9).

Xp21.3 to Xcen

Physical and Genetic Maps

The YAC contig in Xp21 is now complete. The 35 Mb YAC contig of Ferrero et al. (1995) extending from Xp22.3 to Xp21 was connected with the DMD contigs (Monaco et al., 1992 and Coffey et al., 1992). The DMD YAC contigs were linked to YAC contigs in Xp21.1 containing XK, CYBB and

OTC (Nagaraja et al., abst. M6, Meindl et al., abst. M8, Chai et al., abst. M1 and Ho et al., 1994). As indicated on the consensus map (Fig. 1), the order of markers and genes in Xp21 is pter–DXS28–DXS1218–DXS1065–DXS7188–DXS1025–AFMa295za5–DXS704–AFMb277zb1–DXS727–DXS1074–DXS319–AHC–DXS1023–DXS1075–DXS1076–DXS1077–DXS708–GK5'–DXS1078–GK3'–DXS1079–DXS1080–DXS1081–(DXS726,DXS1214)–(DXS503, DXS1234)–DXS268–DXS1241–(DXS239,DXS1036)–((DXS1235–DXS1236),DXS1067)–DXS997–(DXS1237, DXS1219)–DXS1238–DXS269–DXS270–DXS271–DXS164–DXS206–DXS230–DXS272–DXS142–DXS1243–DXS1242–(DXS1014E,DXS84)–DXS196–DXS141–DXS307–(DXS709,DXS6680,DXS6678)–XK–CYBB–DXS140–DXS1082–TCTE1L–DXS1110–DXS352–SCRP1–DXS6679–OTC–DXS1116E–DXS1058–DXS1068–DXS977E–DXS556–AFMa183wf5– cen.

A gap still remains between the proximal end of the Xp21 YAC contig and the Xp11.4 YAC contig reported at the 5th X workshop and recently published by Black et al. (1995). The consensus order is pter–DXS1201–DXS6668–DXS228–DXS77–DXS6669–DXS7–MAOA–MAOB–NDP–DXS6670–RRM2P3–DXS6671–DXS742–cen. Nagaraja (abst. M6) has placed the microsatellite AFMa246ze9 in a YAC contig close to MAOA and NDP.

There is second gap between the YAC contig in Xp11.4 and the large YAC contig reported at the 5th X workshop in Xp11.3–Xp11.23. The latter contig has been published by three groups during the last year (Coleman et al., 1994, Knight et al., 1994 and Hagemann et al., 1994) and is presented with several new markers and genes by Hardcastle et al. (abst. M4), Boycott et al. (abst. M9), Chand et al. (abst. M7), Chai et al., (abst. M1), Meindl et al. (abst. M8) and Derry et al. (abst. M2). The contig has been extended distally to include UBE1 originally suggested by one YAC in Hagemann et al. (1994) and now linked by the gene ZNF157 (Derry et al., abst. M2). PCTK1 has been shown to be within 30 kb of UBE1 (H.F. Willard, personal communication). The large YAC contig in Xp11.3–Xp11.23 has been connected to TFE3 and SYP by one YAC (Chand et al., abst. M7) although several groups could not make this link because of unstable YACs near GATA1. Boycott et al. (abst. M9) has extended their contig proximally to DXS255, merging with the contig reported at the 5th X workshop in Xp11.23 around DXS255 and DXS146 with revised maps in Chand et al. (abst. M7) and Meindl et al. (abst. M8). The order of markers and genes around WASP and GATA1 were subject to much discussion at the workshop and a consensus order was established using YAC and cosmid clones from four different groups.

The following consensus order of markers and genes is derived by the combined physical and genetic maps in the Xp11.3–Xp11.23 region: pter–(UBE1,PCTK1)–ZNF157–DXS1264–DXS1055–DXS1003–DXS1146–DXS337–DXS1266–ARAF1–SYN1–TIMP1–PFC–DXS426–ELK1–DXS1367–ZNF81–ZNF21–DXS1267–DXS6616–(OATL1, SSX1)–DXS7465E–DXS6941–DXS1011E–(WASP, DXS6940)–[(DXS7466E–(DXS7467E,DXS1358), DXS722)]–GATA1–DXS226–HRASP–(DXS1126, DXS1240)–DXS7469E–DXS1470–TFE3–SYP–DXS1007E–DXS7468E–DXS573–DXS1039–DXS6666–DXS255–NPHL–DXS146–DXS6667–cen.

The last gap in YAC coverage is located between the Xp11.23 contig and the 6 Mb YAC contig reported at the 5th X workshop and recently published by Miller et al. in Xp11.22–p11.21(Miller et al., 1995). This contig was reported in part by Chai et al. (abst. M1) and revised by Miller et al (abst. N5) to include new expressed sequences. The consensus order of markers and genes is pter–(OATL2, SSX2)–DXS6672E–DXS1008E–ACTL1–DXS1272E–DXS1000–DXS7461E–DXS988–DXS423E–DXS1204–(DXS7460E, DXS1199)–DXS1013E–FDG1– AFM137xe11–AFMa230vc1–(DXS674,DXS679)–DXS7159E–ALAS2–DXS7462E–DXS991–DXS1302–DXS7463E–DXS741–DXS7464E–DXS579–DXF34S1E–DXS580–DXS429–MTHFDL1–ZXDB–DXS14–DXS422–DXS390a–ZXDA–DXZ1.

New genes in the Xp11.23 YAC contig

Several groups have isolated and mapped new genes in the Xp11.23 YAC contig near WASP, GATA1, TFE3 and SYP. Meindl et al (abst. M8) mapped two newly isolated genes, DXS7469E (xp664, Wehnert et al., abst. A4), and DXS7468E (T54) in this region and they are included in the consensus map. Several genes isolated by Geraghty et al. (Geraghty et al., 1993) by whole YAC hybridization to cDNA libraries have been mapped by several groups onto the YAC and cosmid contigs in this region. They include DXS7465E (MG61), DXS7466E (MG44) and DXS7467E (MG21) and have been included in the consensus map. Derry et al., (abst. M2) have isolated a number of new genes (DXS7476E, IS2; DXS7477E, IS7; DXS7478E, RNPL) from the same region using cDNA selection, one of which (IS6) is identical to DXS7466E (MG44). Boycott et al. (abst. M9) has isolated two new genes in the same region by cDNA selection and they are designated DXS7472E (PU3) located between GATA1 and TFE3, and DXS7471E (PU1) located between SYP and DXS255.

New genes in the Xp11.22–p11.21 YAC contig including genes which escape X-inactivation

Miller et al. (abst. N5) have used cDNA selection to isolate a number of new genes across their 6-Mb YAC contig in Xp11.22–p11.21 (Miller et al., 1995). These include DXS7461E (XCL17), DXS7460E (IB722, URE–B1), DXS7159E (HSC0AA062, Xp11B6), DXS7463E (EST14620, YY1L1), and DXS7464E (QP-C,WI-7092). Miller et al. have also characterized the X-inactivation status of several known genes mapping in this YAC contig. Two genes in this region had already been shown to escape X-

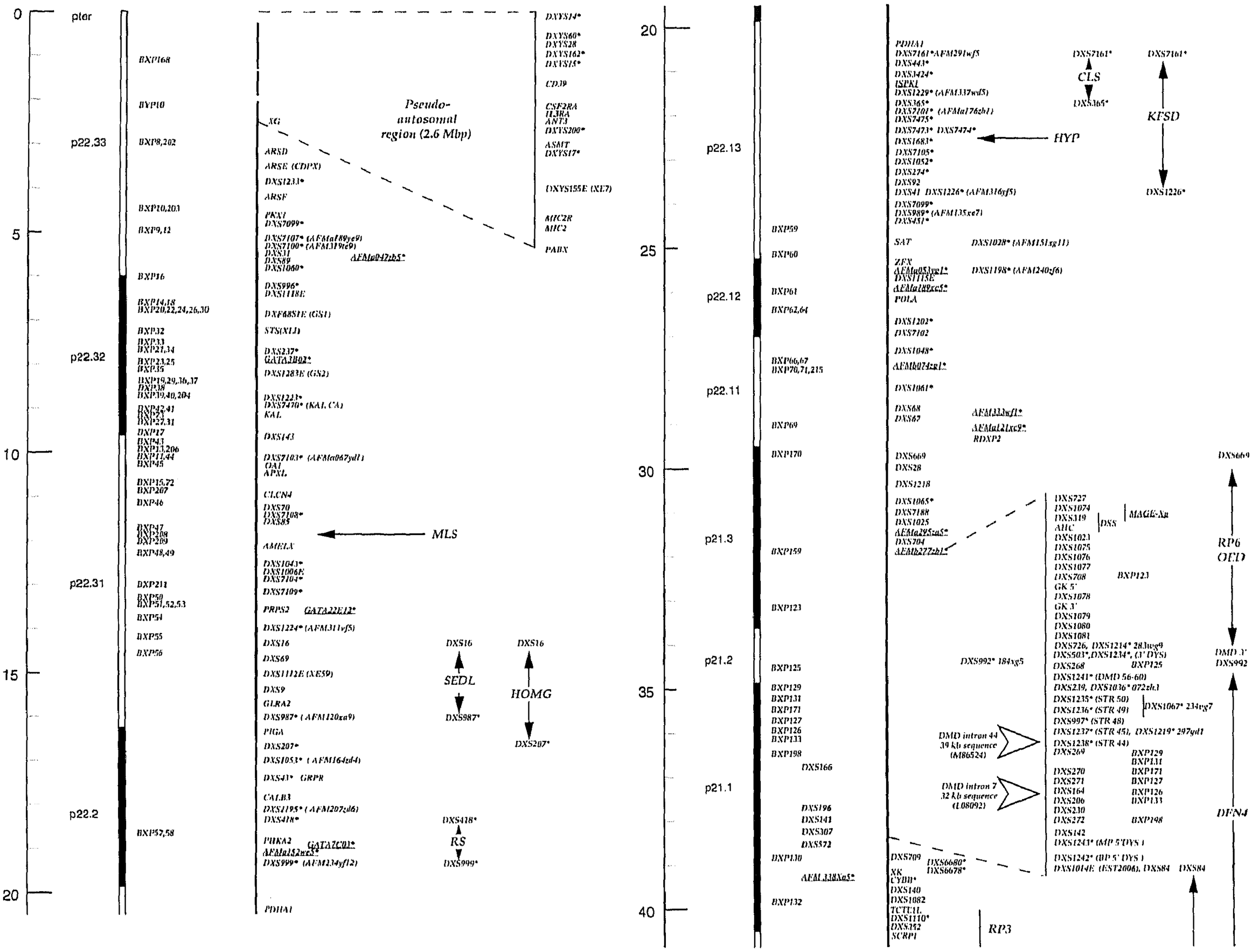
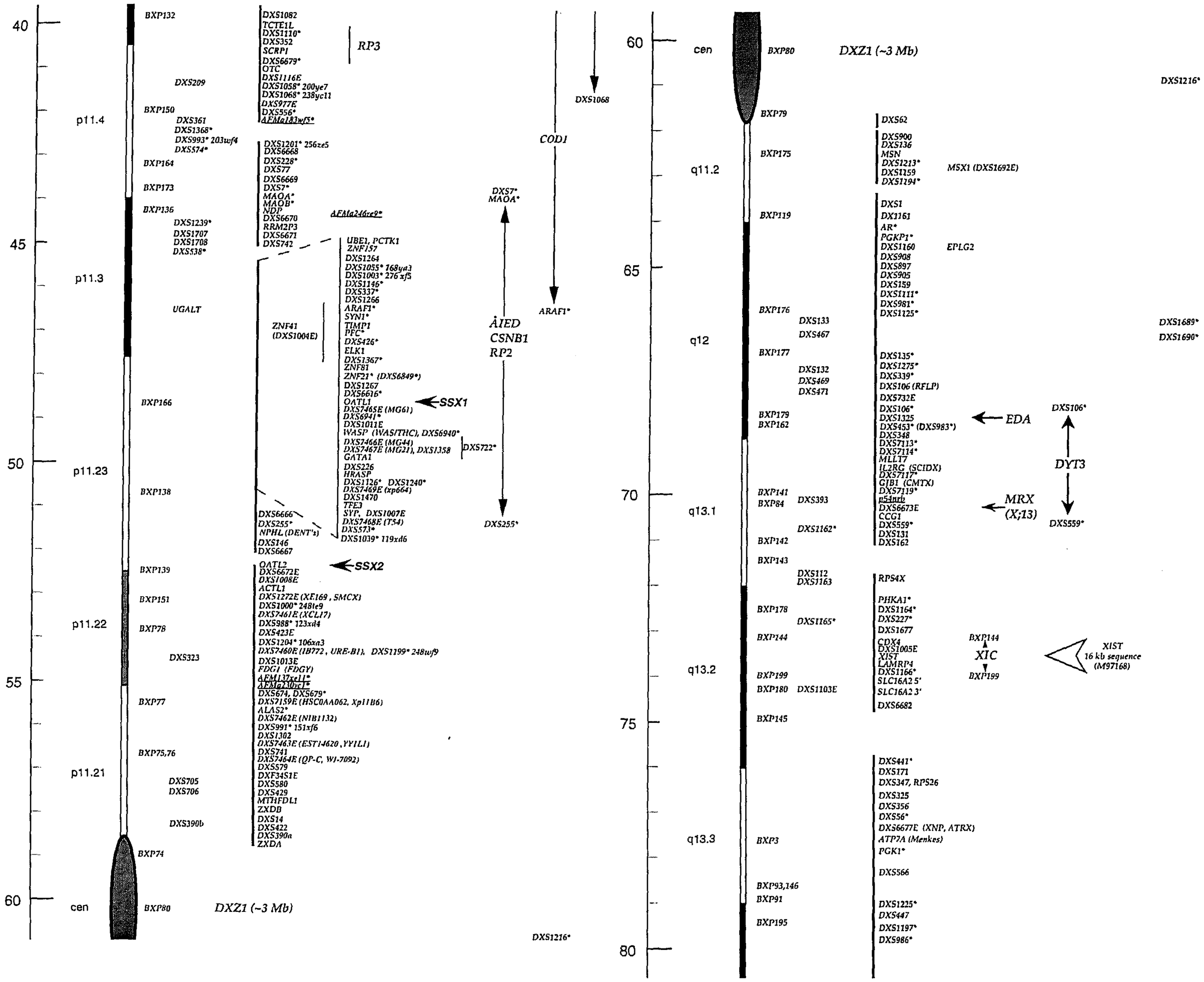


Fig. 1a. X chromosome physical map. This map represents a compilation of information regarding physical mapping of the chromosome from a variety of sources and interpreted by the X chromosome editors. The map is based on a previous map published in the XCW5 report. Some anonymous DNA markers present on prior maps have been removed due to space constraints, however all genes and highly polymorphic markers with well-established position and order are shown. Anonymous markers, genes and breakpoints are indicated in order along the chromosome relative to an arbitrary scale approximating the distance from pter to qter in megabases of DNA. Approximate location of cytogenetic bands is also indicated. Loci with highly informative microsatellite repeats are indicated with asterisks. YAC contigs are indicated by vertical bars; those closest to the chromosome are drawn approximately to scale. Some contigs are expanded to show detail; these are indicated by dashed lines connecting the bars. Support for the order of objects shown on the YAC contigs is very high. DNA segments and genes shown to the left of the YAC contigs are ordered relative to breakpoints, but usually do not have a consensus order relative to other markers in the same interval, or with markers shown in YAC contigs. Breakpoints in some regions are indicated twice: once next to the chromosome to maintain the linear order, and again in the relevant YAC contigs. Phenotypes for which genes have not yet been identified are indicated in large type, often on double-arrowhead lines to indicate the region in which the gene resides. Horizontal arrowheads are used for phenotypes with very high probability locations between markers in the map. Objects (microsatellites and expressed sequences) to the extreme right of the figure have not been placed into the physical map with high confidence, but are deemed important by the editors and are therefore indicated with the expectation that they will be placed into the next version of the map by interested groups. Large arrowheads are used to indicate regions of significant sequence data. A number of map objects are not represented in the current version of GDB; these are highlighted with underlining. These are designated with various nomenclatures. Some markers from the AFM series of microsatellites from the CEPH/Genethon effort are shown without DXS numbers, as these are as yet unassigned. In addition, in some regions, the AFM designator has been provided adjacent to its DXS number for added clarity.



inactivation including DXS1272E (XE169, SMCX; Wu et al., 1994 and Agulnik et al., 1994) and DXS423E (Brown et al., 1995). Miller et al. (Miller et al., 1995) showed that DXS10008E, DXS6672E and DXS1013E are subject to normal X-inactivation while SSX1 escapes X-inactivation. Given the order of these genes in their contig as Xpter–SSX1–DXS6672E–DXS1008E–DXS1272E–DXS423E–DXS1013E–Xcen it is clear that genes which escape X-inactivation are interspersed with genes that are subject to X-inactivation.

Mapping and Isolation of Disease Genes

A family has been identified with X-linked dominant sensorineural hearing impairment (DFN4), characterized by incomplete penetrance and variable expressivity in carrier females. Linkage analysis has given a tentative localization in Xp21.2 with a two-point LOD score of 2.91 at DXS997, within the DMD gene (Lalwani et al., 1994). DMD patients are not known to have any associated deafness. The distal flanking marker was DXS992 placed by linkage between the 3' end of DMD and exon 50, and by STS analysis of DMD YACs by Chai et al., (abst. M1), although Nagaraja (abst. M6) could not place DXS992 within the DMD YAC contig. The proximal flanking marker was DXS1068, which is just centromeric to OTC in Xp21.1.

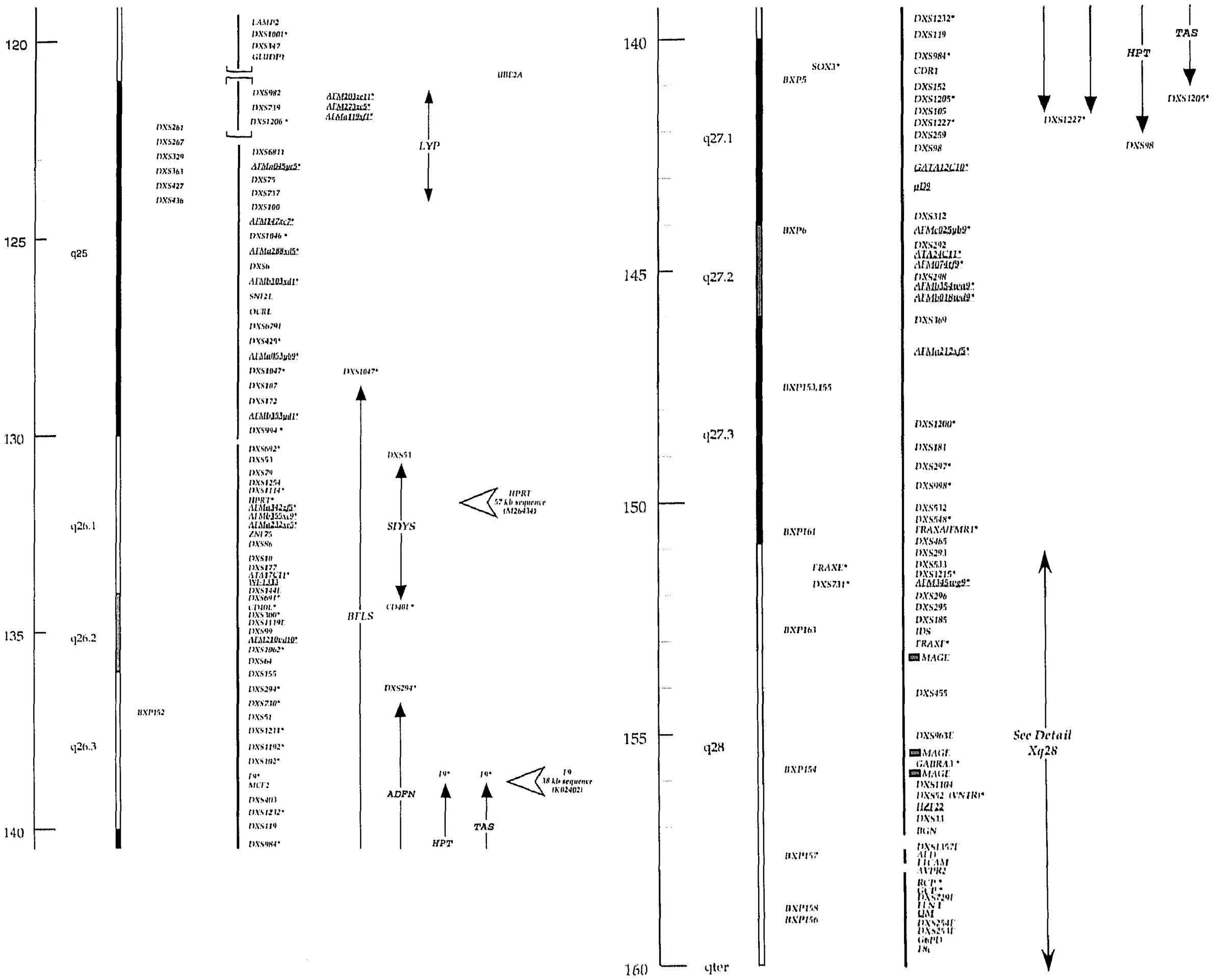
The position of a gene defective in X-linked progressive cone dystrophy (COD1) has been refined in a single large pedigree by Hong et al. (Hong et al., 1994). It is most likely located between DXS84 and ARAF1 in Xp21.1–p11.3. A new Dutch family with congenital stationary night blindness (CSNB) has been mapped to Xp21.1 in the same region as retinitis pigmentosa (RP3), indicating a possible relationship (Bergen et al., 1995). The flanking markers were DXS1238 in the DMD intron 44 distally and DXS228 proximally. Linkage analysis in a second Dutch family with CSNB has shown linkage in the Xp21.1–p11.23 with flanking markers of OTC distally and DXS1003 proximally (Berger et al., 1995). The strongest linkage was in the DXS228, MAOB and

NDP region in Xp11.4–p11.3 although no mutations were found in the NDP coding region. As outlined in previous reports, other families with CSNB have been linked between MAOA and DXS255 (CSBN1 on the map) thus indicating that there are at least three different locations for genes determining this phenotype in Xp21–cen. Perhaps the CSNB phenotype is allelic to other eye diseases in this region such as RP3, RP2 and AIED. This will only become clear when candidate genes are isolated and tested for mutations in these families with X-linked eye diseases.

A new conserved gene (SCRP1; GDB G00-586-661) has been isolated in the RP3 critical region between TCTE1L and OTC in Xp21.1 which is highly expressed in retina with similarity to cell adhesion proteins with short consensus (sushi) motifs (Meindl et al., abst. M8). So far no mutations have been identified in RP3 patients.

Several disease genes have been positionally cloned in the Xp21–cen region during the last year including adrenal hypoplasia congenita (AHC), Wiscott-Aldrich syndrome (WAS), Dent's disease (NPHL), Aarskog-Scott syndrome (Faciogenital dysplasia, FGDY) and genes at translocation junctions in synovial sarcomas.

As reviewed in previous workshop reports, adrenal hypoplasia congenita (AHC), often associated with hypogonadotropic hypogonadism (HH) maps by deletion analysis in Xp21.3 just distal to glycerol kinase deficiency (GK). A candidate gene for AHC was isolated by Zanaria et al. (Zanaria et al., 1994) using a conserved CpG island in the AHC deletion interval which overlaps partially with the critical region for dosage sensitive sex reversal [DSS, (Bardoni et al., 1994)]. The gene, termed DAX-1 (DSS, AHC, X-linked gene 1), is a novel member of the nuclear hormone receptor gene family expressed in adrenal glands



and testis and is mutated in patients with both AHC and HH (Zanaria et al., 1994 and Muscatelli et al., 1994). DAX-1 has a novel N-terminal DNA binding motif which can bind to the retinoic acid response element (RARE) and act as a dominant negative regulator of transcription mediated by the retinoic acid receptor (Zanaria et al., 1994). In six cases of AHC no mutations were found in DAX-1 indicating that there may be genetic heterogeneity (Muscatelli et al., 1994). Another gene cluster was isolated by exon amplification in the DSS critical region, 50 kb distal to DAX-1 with strong homology to the MAGE cluster of 12 genes located in Xq27–qter (Muscatelli et al., abst. B10). There was a minimum of 5 MAGE-Xp genes in a 30 kb interval, one of which was completely sequenced and found to be expressed normally in testes but not in any tumor tissues tested.

The gene for Wiscott-Aldrich syndrome (WAS) has been isolated and reported by Derry et al. (Derry et al., 1994). As described in the 5th X chromosome workshop, the WAS gene had been located by linkage analysis between DXS255 and genetic markers just proximal to the gene cluster ARAF1–TIMP1–PFC–ELK1. Derry et al. (Derry et al., 1994) constructed a YAC and cosmid contig linking the flanking genetic markers and including the gene for GATA1. They used cDNA selection on YACs and cosmid clones in this interval to isolate seven distinct transcription units. One of these cDNAs, named WASP, was restricted in expression pattern to cell lines of lymphocytic and megakaryocytic origin, thymus and spleen and found to be absent in B-lymphoblastoid cell lines from two patients with WAS. The full length cDNA was 1820 bp with an open reading frame of 502 amino acids. The predicted protein was generally hydrophobic and proline rich but had no similarities to known proteins in the database. The genomic structure of the gene was determined to contain 12 exons and 11 introns

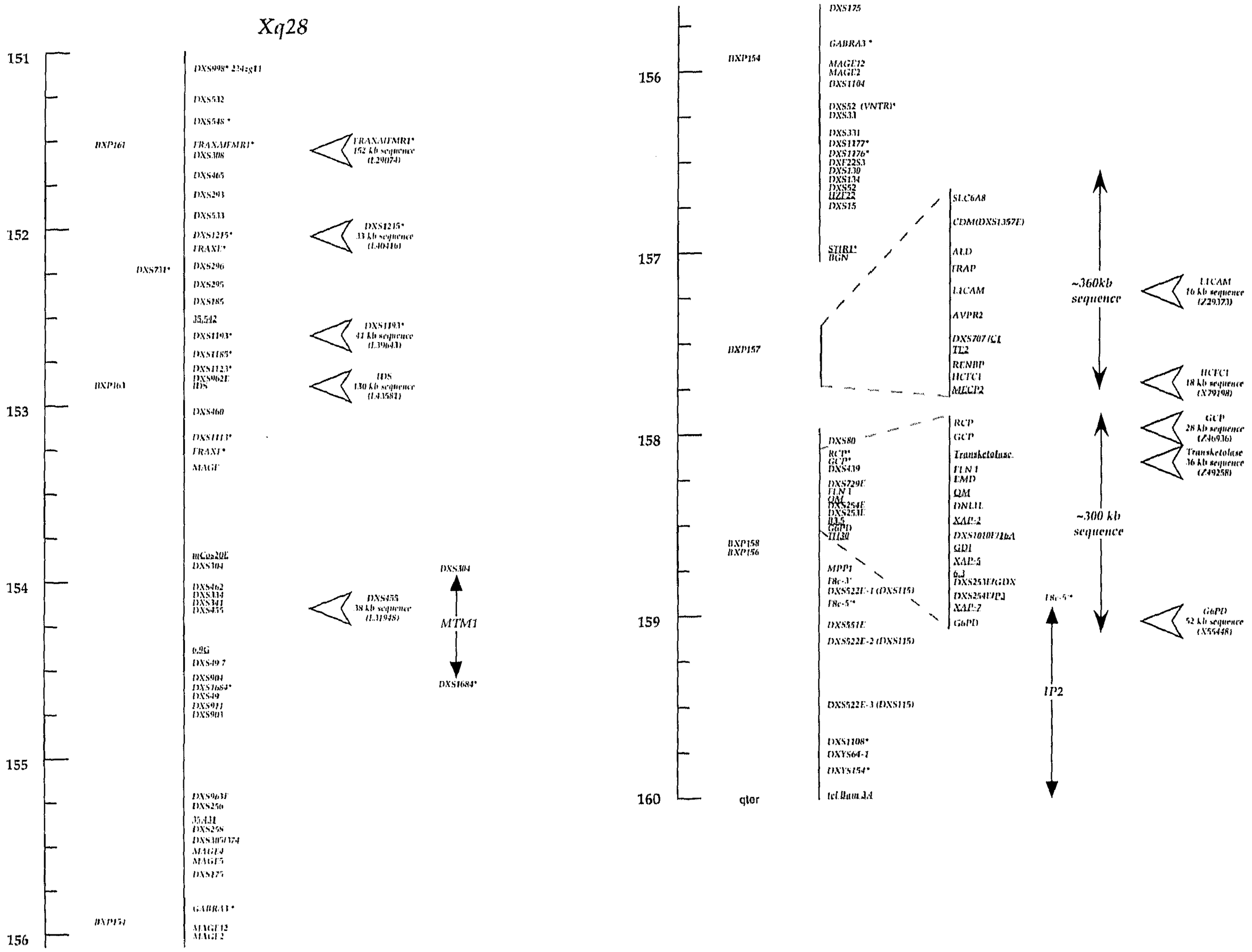


Fig. 1b. Xq28 detailed map. Due to the complexity of information in this region, Xq28 has been expanded approximately 5-fold in a separate figure. The conventions of Fig. 1a apply to this figure as well. Large arrowheads are used to indicate regions of significant sequence data. A number of novel genes are indicated in the distal portion of the map; those with more than one symbol are indicated as (X/Y).

spanning 9 kb. Proof that WASP was the correct gene was obtained from nine independent mutations found in unrelated WAS patients (Derry et al., 1994), abst. M2) and in 12 unrelated WAS patients (Kwan et al., 1995). More recently, the WASP gene has been found by Villa et al. (1995, abst. M5) and Derry et al. (abst. M2) to be mutated in several patients with X-linked thrombocytopenia (THC) with small-sized platelets. These data demonstrate that THC and WAS are allelic forms of the same disease.

A candidate gene for Dent's disease (hereditary nephrolithiasis, NPHL) has been described by Fisher et al. (1994) in Xp11.23. The gene is a member of the CIC family of voltage-gated chloride channels and is expressed predominantly in the kidney and is a strong candidate based on absence from patients with microdeletions. This gene is currently being tested for mutations in nondeletion patients.

A recurrent translocation junction [(t(X;18)(p11.2;q11.2)] involved in synovial sarcoma has been isolated by Clark et al. (1994), and a gene (SSX) has been identified from the region near OATL2 of the X chromosome involved in the translocation. A combined 18:X cDNA is expressed in these tumors, however its function is as yet obscure. As reviewed in previous X workshop reports, there are two distinct synovial sarcoma breakpoints, one near OATL1 and one near OATL2. Recently a histological sub-classification shows differences in the tumor type depending on location (Renwick et al., 1995). Using RT-PCR on RNA extracted from a series of independent synovial sarcomas, both Crewe et al. (1995) and de Leeuw et al., (1995) have isolated distinct X chromosome

sequences with unique SSX1 sequences for translocations near OATL1 and SSX2 sequences near OATL2. The SSX1 and SSX2 genes encode closely related proteins (81% identity) of 188 amino acids with the N-terminal portion exhibiting homology to the Kruppel-associated box (KRAB), a transcriptional repressor domain previously found only in Kruppel-type zinc finger proteins (Crewe et al., 1995). Analysis of YAC contigs around the SSX1 and OATL1 region has shown that the SSX1 gene is present in at least five copies all mapping within a 275-kb region (Chand et al., abst. M7).

A gene (FGD1) involved in Aarskog-Scott syndrome or faciogenital dysplasia (FGDY) has been identified by Pasteris et al. (1994). This gene product would appear to be a guanine nucleotide exchange factor of the rho/rac variety. It is interrupted in a female patient with a reciprocal translocation (X;8) in the region between ALAS2 and DXS323 and presenting the clinical phenotype. This woman also transmitted the phenotype and the translocation to a son. Mutations in this candidate were observed in a second family, offering confidence that this is the gene responsible for the syndrome.

Xcen – Xq13.3

Physical/genetic map

Efforts mainly by two groups are continuing to press this region toward closure in YACs. Villard et al. (abst. N2) presented evidence that three prior gaps were closed, extending their prior published results (Villard et al., 1995). Other gaps remain difficult due to instability (between MSN and DXS1; the interval between DXS106 and DXS453, and a third region between DXS169 and DXS995). Miller et al. (abst. N5) reported four contigs in the proximal portion of the region composed of 61 YACs and 45 STSs. Three gaps remain in this effort, one of which (AR to PGKP1) was reported closed by Villard et al. (abst. N2). Haberhausen et al. (abst. N1) reported a contig composed of 14 YACs spanning DXS453 to DXS131 that substantially refines positions of markers and genes in this interval (see below). Despite this considerable progress, the region remains thin in many spots, and additional effort will be required to complete the map.

Additional highly polymorphic markers have been placed or refined in the region and these are noted by asterisks on Fig. 1. One in particular (DXS1178) was shifted from Xp21.1 apparently wrongly positioned due to YAC chimerism (Fujita et al., 1995). Additional markers have been reported by Haberhausen et al. (abst. N1) and by Weeks et al. (1995) who report a high resolution genetic linkage map of the pericentromeric region and compare it with the physical map from XCW5. They found an overall correspondence of 2 cM per megabase, with two regions of reduced recombination. The integrated 2-d map of Fain et al. (1995) shows a marker order consistent with that of the physical map, with the exception of DXS1275. The genetic distance from the Fain et al. map is 9 cM.

Novel genes

Several novel genes have been placed in the region. A member of the transmembrane 4 superfamily of proteins has been assigned to Xq11 using somatic cell hybrids (Virtaneva et al., 1994). This gene was termed MXS1 and has been previously described as CCG-B7 (DXS1692E) by Li et al. (1993).

EPLG2, a high affinity binding protein for the receptor tyrosine kinase Elk, has been placed immediately distal to PGK1P1 through YAC hybridization by Fletcher et al. (1995). The gene had previously been linked to AR in the mouse. Two genes have been assigned to the interval under investigation for DYT3. The first, termed CD1 by Haberhausen et al. (abst. N1) and AFX1 by Parry et al. (1994) is a member of the forkhead gene family. Its GDB designation is MLLT7. These genes are related to the Drosophila homeotic gene forkhead, and numerous human hepatocyte transcription factors are found to carry a similar protein motif. Parry et al. found the gene adjacent to a translocation junction t(X;11) (q13;q23) recovered from an infant with acute lymphocytic leukemia. Haberhausen et al. (abst. N1) have positioned the gene on YACs which place it immediately proximal of IL2RG. They have also determined that the gene is composed of at least three exons and shows highest expression in skeletal muscle and placenta, consistent with the study of Parry et al. (1994).

A previously known gene has been placed into the DYT3 interval by the work of both Haberhausen et al. (N1) and Villard et al. (abst. N2). This is known as $_{p}54^{nrb}$. Dong et al., 1993, Haberhausen et al. (abst. N1) and Villard et al. (abst. N2) report localization between GJB1 and CCG1 and that the gene is composed of at least seven exons and is ubiquitously expressed. Both genes are considered candidates for DYT3 (see below).

A member of the caudal family of homeobox genes, CDX4, has been localized in Xq13.2, within 400 kb proximal to XIST, based on YAC associations (Horn and Ashworth, 1995). In the mouse, this gene is found within 100 kb of Xist. The gene previously identified with the anonymous marker DXS128, and known in the last report as XPCT has received its official name, SLC16A2.

Villard et al. (abst. N2) report additional cDNAs obtained by cDNA selection using YACs from the region. These include A9 (between DXS1 and AR), E2 (between RPS4X and PHKA1), G5 (between DXS325 and DXS356), A8 (between DXS356 and DXS56), IL4 (between ATP7A and PGK1) and J15 (between PGK and DXS447). Some of these have been described previously in publications (Gecz et al., 1993; Villard et al., 1995). Other expressed sequences have been localized to the region by the EST mapping efforts of Gianfrancesco et al. (abst. A7), however they are not yet integrated into the YAC contig.

Disease genes

Haberhausen et al. (abst. N1) have refined the interval for DYT3 through association studies with novel microsatellites. They find significant association with markers DXS7717 and DXS7719, suggesting a placement of the gene in the vicinity of IL2RG, GJB1 and CCG1. This interval is the location of two newly placed genes described above.

The gene defective in alpha-thalassemia with X-linked mental retardation (ATRX) was found to be the previously described XNP gene (DXS6677E), a presumptive regulator of transcription (Gecz et al., 1994; Gibbons et al., 1995; Stayton et al., 1994). The defect would appear to affect expression of multiple genes, including the alpha globin genes.

A mutation in the alpha subunit of the muscle isoform of phosphorylase kinase (PHKA1) was reported in a patient with muscle glycogenosis by Wehner et al. (1994)). This is the first description of a mutation in this gene in humans.

Novel linkage to the Xcen region (DXS7 to DXS441) was reported by Orth et al. (abst. N4) for a disorder in a large Lebanese family showing congenital failure of autonomic control of ventilation (CEPA), a condition similar to the Ondine curse, an autosomal recessive trait.

Xq21–q25

Physical and Genetic Map

Most progress with respect to the physical map has been made in the Xq21–q22 region which has been cloned in a contiguous 30 Mb contig through the combined efforts of several groups (Colleaux et al. abst. C1; Kendall et al. abst. C6; Mumm et al. abst. C3 & C4; van der Maarel et al. abst. C2, (1995); Sala et al. abst. C13; Sargent and Affara, abst. C14; Srivastava et al. 1995; Stanier et al. personal communication; Sweatman et al. 1994). At the proximal side, this contig links up to a previously published YAC contig spanning PGK1 at Xq13.3 (Villard et al. 1995). The 30-Mb contig contains a very detailed map of the critical region for cleft lip & palate (Stanier et al. personal communication), as well as the X–Y homology region (Mumm et al. abst. C4; Sargent & Affara, abst. C14). The latter region measures 3.5 Mb and contains a small internal X-chromosomal specific segment defined by DXS214. At the distal side, the contig extends just distal to the COL4A5 and COL4A6 genes (Srivastava et al. 1995). Construction of the Xq21–q22 YAC contig was facilitated by deletions and X-autosome translocation breakpoints which were used to order VNTR markers and STSs from YACs in 22 distinct intervals (Philippe et al. 1995). In Xq22, the contig contains the previously described 6.5-Mb YAC contig spanning the BTK and GLA genes (Vetrie et al. 1994). The only marker from this contig which yielded conflicting mapping results is DXS326, which was mapped proximal to the ZNF6 gene by Van der Maarel et al. (abst. C2), and distal to ZNF6 by Colleaux et al. (abst. C1). Genetically, DXS326 was mapped proximal to DXS1209 by Fain et al. (1995).

In Xq23–q25, YAC mapping is in progress. Seven variably sized YAC contigs were presented by Nagaraja et al. (abst. C10), Porta et al. (abst. C9), and Steingruber et al. (abst. C7). In addition, a number of Genethon markers were mapped in Xq23 and used to isolate novel YACs. Since several markers from this region gave conflicting mapping results, the proposed order is tentative. This also holds true for some of the loci mapping in deletions associated with X-linked lymphoproliferative disease (LYP) (DXS982, DXS739, DXS1206). Distal to this region, a 7-Mb YAC contig was constructed between DXS6811 and DXS994. Conflicting map locations were reported for DXS425 and DXS1212, which were linked to the OCRL and DXS6791 loci distal to the LYP region by Nagaraja et al. (abst. C10). In contrast, Steingruber et al. (abs C7) assigned DXS425 proximal to the LYP region and the ANT2 gene, and the DXS1212 locus just distal to the ANT2 gene and proximal to the LYP region.

In comparison with the genetic map published recently by Fain et al. 1995, there are a few discrepancies. DXS1106, located just distal to the PLP gene at Xq22.2 in the physical map, is located proximal to the DXS366 locus at Xq22.1 by Fain et al. (1995). In the latter study, the order of the DXS1230 and DXS1120 loci is reversed compared to the indicated order (see consensus map) proposed by Kendall et al. (abs C6) which is based on YAC mapping. Fain et al. (1995) map DXS425, together with DXS42, 7 cM proximal to DXS100.

The total physical size of the Xq21–q25 region, 50 Mb, matches the genetic size of this region, 50 cM, as determined by Fain et al. (1995). However, recombination frequencies seem to be lower in the Xq13.3–q21.31 region, approximately (0.5 cM per Mb), and higher in the Xq21.32–q25 region (2 cM per Mb).

Localized disease and normal genes

The identification of novel deletions associated with mental retardation and choroideremia have lead to different assignments of a gene underlying mental retardation at Xq21.1. Studies by Van der Maarel and coworkers suggest a location near DXS232, just distal to the POU3F4 gene (Van der Maarel et al. 1995; abs C2). In their study the critical region at the distal side is demarcated by a deletion associated with classical choroideremia. Colleaux and coworkers propose a more distal location for the MR gene between the DXS233 locus and the CHM gene based on the identification of a novel deletion associated with MR and CHM (abs C1). The putative MR gene at Xq21.1–q21.2 might also be disrupted by a paracentric inversion X(q21.2q24) associated with mental retardation, which was recently described by Abeliovich et al. (1995).

Genetic linkage studies by Gorski et al. (1994) and Forbes et al. (1995) assigned the gene underlying cleft palate and

ankyloglossia (CPX) to a chromosomal segment flanked by the loci DXS1002 and DXYS1X. Gorski et al. (1994) employed a polymorphic marker, DXS1109, which maps between DXS447 and DXYS1X, but which has not yet been mapped into the YAC contig. An X-linked recessive deafness syndrome with blindness, dystonia, fractures, and mental deficiency (DFN-1), was localized to the Xq21.33–q22.3 region between the loci DXS990 and COL4A5 (Tranebjaerg et al. 1995; S. Schwartz, personal communication). The gene underlying congenital generalized hypertrichosis (CGH) was mapped to a large interval at Xq24–q27.1, which at the proximal side is flanked by the marker DXS425, and at the distal side by DXS1227 (Figuera et al. 1995).

Powell et al. (1994) and Sala et al. (abs C13) studied one case and 6 cases respectively of balanced X-autosome translocations in women with premature ovarian failure (POF), but with stature in the normal range and no Turner stigmata. Using Southern blot analysis of somatic cell hybrids containing individual translocation chromosomes or by in situ hybridization analysis of YAC clones, the X-chromosomal translocation breakpoints were mapped throughout the Xq21 region. Unless position effects are responsible for POF, these findings seem to rule out the involvement of one gene in Xq21 in ovarian development.

The mouse *Brain-4* gene, encoding a POU domain transcription factor, was genetically mapped between the mouse *Pgk1* and *Plp* genes (Douville et al. 1994). The human homolog of this gene, POU3F4, was subsequently mapped at Xq21.1, in the critical region for DFN3 (de Kok et al. 1995; see below). The human protein kinase C iota gene (PRKCI) was mapped approximately 150 kb distal to the BTK and GLA genes (Mazarella et al. 1994).

A novel gene, ANT2, encoding the adenine nucleotide translocase 2 protein was mapped in Xq24–q25 close to DXS425 (Schiebel et al. 1995). Since the exact location of DXS425 is not yet clear (see above), the location of ANT2 remains to be investigated in more detail. A novel gene, the lymphoid proliferation-associated gene EPAG (Bennett et al. 1994), was mapped in Xq21–q22 by Dizikes et al. (1995). The angiotensin II receptor (AGTR2) gene was mapped to chromosome Xq22–q23 by fluorescence in situ hybridization (Chassagne et al. 1995).

Genes that were mapped in the Xq21–q25 interval some years ago and which have not yet been mapped in YAC contigs include the farnesyl diphosphate synthetase-like 5 (FDPSL5) and teratocarcinoma-derived growth factor 2 (TDGF2) genes at Xq21–q22, the avian myelocytomatosis viral (v-myc) oncogene homolog 2 (MYCL2) gene at Xq22–q28, the 5-hydroxytryptamine (serotonin) receptor 1C (HTR1C) gene at Xq24, and the ubiquitin-conjugating enzyme E2A (RAD6 homolog) (UBE2A) gene at Xq24–q25.

Disease genes

Five minideletions associated with X-linked deafness (DFN3) were identified (Huber et al. 1994; Bitner-Glindzicz et al. 1994; Piussan et al. 1995; Dahl et al. 1995) which enabled the fine mapping of the critical region for DFN3 into a 850-kb cosmid contig (Huber et al. 1994). The human homolog of the mouse *Brain 4* gene, POU3F4, was mapped in the critical region and found to contain small mutations in its POU domain in 7 of 9 unrelated DFN3 patients tested (de Kok et al. 1995; Bitner-Glindzicz et al. 1995). The POU3F4 gene encodes a transcription factor which belongs to a large protein family. Surprisingly, the intronless POU3F4 gene is located up to 500 kb distal to 4 of the 5 DFN3 associated minideletions. In one DFN3 patient, a duplication/inversion was identified. The duplicated segment measures 150 kb the endogenous copy of which is located 170 kb proximal to the POU3F4 gene. Southern blotting, PFG analysis, and FISH analysis suggest that in addition to the duplication, a paracentric inversion occurred which displaced one copy of the duplicated segment, as well as the POU3F4 gene, to a more distal location near Xq21.3 sequences (de Kok et al. abs C5). This finding indicates that in the patients with minideletions or the duplication/inversion involving sequences proximal to the POU3F4 gene, the POU3F4 gene is silenced through position effects or through the deletion or displacement of a regulatory element located more than 500 kb proximal to the POU3F4 gene.

In choroideremia patients, approximately 30% of cases show variably sized deletions (Van Bokhoven et al. 1994a and b; Van den Hurk et al. unpublished results). In approximately 40% of patients, small mutations were identified which invariably result in premature termination of protein translation (Van Bokhoven et al. 1994b). In only one case, a missense mutation was identified in the CHM gene (Donnelly et al. 1994). However, in the latter study, exons 1 through 10 were not investigated which leaves the possibility that a second mutation is present in the open reading frame of the CHM gene that results in carboxyterminally truncated CHM protein.

In several studies the BTK gene was analyzed in patients with X-linked agammaglobulinemia (Conley et al. 1994; Hagemann et al. 1994; Gaspar et al. 1995; Jin et al. 1995; Vorechovsky et al. 1995). Although different types of mutations (missense, nonsense, splice) were found, no apparent correlation between the genotype and phenotype could be made since considerable intra- and interfamilial variability was observed. Some residues, as e.g. the Arg and Met codons at positions 520 and 630 respectively, were found to be mutated in a number of apparently unrelated cases. Patients with a mild phenotype diagnosed as common variable immune deficiency (CVID) were found to contain either small mutations in the BTK gene or a deletion spanning the carboxyterminal end (exons 17, 18, and 19) of the gene (Vorechovsky et al. 1993; Ohta et al. 1994).

In Fabry disease, an X-linked inborn error of glycosphingolipid catabolism, mutation analysis was performed in the causal gene, alpha-galactosidase A (Eng et al. 1994). Small, unique mutations were found throughout the

7 exons of this gene; however, codons 111–122 defined a deletion hot-spot. Also, the Arg112His mutation resulted in residual activity and a mild variant phenotype in one patient.

Hodes et al. (1995) reported on a heterozygous mutation in exon 2 of the PLP gene in a female which resulted in Pelizaeus-Merzbacher disease.

Previously, the association between Alport syndrome (AS) and diffuse oesophageal leiomyomatosis (DL), a smooth muscle cell tumor, was shown in patients with deletions in the COL4A5 and COL4A6 genes (Antignac et al., 1992; Zhou et al. 1993). In a study by Heidet et al. (1995), it was shown that in 7 patients with DL and AS, the deletions encompass only the first two exons of the COL4A6 gene and variable parts of the 5' end of the COL4A5 gene. In 3 patients with AS without DL, the deletions encompass a larger segment of the COL4A6 gene and variable parts of the COL4A5 gene. These results suggest that DL-AS could be caused by a truncated alpha6(IV) chain.

Long range sequencing

Nagaraja and coworkers (abs C11) reported on the sequencing of a 160-kb human YAC clone (yWXD703) containing the ANT-2 gene by ordered shotgun sequencing. Partial *Sau*3AI fragments in the 6–9 and 9–15 kb range were subcloned and the inserts were amplified using a modified long-range PCR protocol. End sequences from 140 clones were used to assemble a preliminary map and minimally overlapping inserts were selected for shotgun cloning in M13 after sonication. 140 kb of the YAC has been assembled and the remaining parts are in smaller contigs with overall 99% data precision.

Oeltjen et al. (1995) sequenced 69 kb of contiguous human genomic sequence containing the alpha-galactosidase A and Bruton's tyrosinase kinase loci. Cosmid DNA was sonicated, blunt ligated to adaptors, size fractionated to 1.5–2.5 kb, and ligated into a modified M13 vector. Assembly of the complete sequence was complicated by the presence of 49 full and partial Alu repetitive elements. Apart from the genes indicated above, the 69-kb sequence (Genbank accession number L35265) contained two open reading frames. The gene previously mapped between the GLA and BTK genes was labeled DXS1273E (Vorechovsky et al. 1994). The putative 106-amino acid polypeptide shows 99% amino acid sequence identity with a human ribosomal protein homologous to the yeast L44 ribosomal protein. The second novel gene was designated DXS1271E, and most likely encodes a 449 amino acid hnRNA binding protein (Vorechovsky et al. 1994).

Xq26–qter

Physical/genetic map and evolutionary comparisons

The entire region of Xq26.1–qter is now organized in long-range contiguous coverage in YACs, with some supplementary recovery of delimited gaps in Xq28 ongoing with bacterial clones. The published 8-Mb contig spanning Xq26 (Little et al., 1993) has been fitted with 88 STSs and extended 1 Mb to DXS53 at its centromeric end, and is merged with the Xq27 contig (S3) (Pilia et al., ms. in preparation). The Xq27 contig (12 Mb and 120 STSs) then continues the cloned coverage and links up with the previously analyzed 7.1 Mb of Xq28 YAC maps provided by Palmieri et al. (1994, fitted with 68 STSs), and by Rogner et al. (1994).

The genetic maps of Fain et al. (1995), Donnelly et al. (1994), Gyapay et al. (1994) and J. Weissenbach, (personal communication) have been compared to the physical map across the distal 30 Mb of Xq, with general concordance of marker order. In the most centromeric 5 Mb of Xq26 relatively low recombination has been observed, with recombination values then rising to about 2 cM/Mb from about DXS296 to the telomeric region.

For the subregion of Xq27–q28, between coagulation factors IX and VIII, the syntenically equivalent mouse segment of the X chromosome has been comparatively analyzed. The tools generated include a 2.3-Mb YAC contig spanning from *Gabra3* to *G6pd* on the mouse X (Chatterjee et al., 1994) and a comparative map between IDS and DMD on the mouse X compared to the human Xq28 (P3).

In a different type of comparative analysis, a gene-rich duplication between Xq28 and 16p11.1 has been analyzed by Eichler et al. (S8). A region of about 35 kb has been duplicated, with orthologs of several genes (see below) identified on cosmids from both chromosomes; >30 kb of directly sequenced material shows >95% sequence identity. Hybridization evidence further indicates that pericentromeric regions of other primates have also received versions of the same region.

Gene searches in the region based on the map

Both the large number of genes and disease genes, particularly in Xq28, and the availability of the map, have facilitated increasingly extensive analyses of gene content in this region.

Localized disease and normal genes

One gene added to the catalogue for the region is hereditary bullous dystrophy (X-linked macular type), assigned to Xq27.3–qter (Wijker et al., 1995). Also approximate in its localization is the calcium ATPase isoform 3 (ATP2B3), which is assigned only to Xq28 (Wang et al., 1994a). Weaker linkage analysis still yields uncertain localization of a possible bipolar disorder gene in Xq28 (Baron et al., 1994).

As for more highly localized genes, starting from Xq26 and moving toward the telomere, refined mapping of the human CD40L gene has placed it between DXS144E and DXS300 (Pilia et al., 1994; see consensus map), and additional novel mutations have been reported that produce

the Hyper IgM syndrome (Macchi et al., 1995; Shimadzu et al., 1995).

Linkage analysis of six polymorphic loci by Dixon et al. (abst. S1) has placed X-linked recessive hypoparathyroidism in a most likely interval between Factor IX and DXS98 (Xq26.1– q27). Joseph et al. (abst. S2) place X-linked albinism-deafness (ADFN) in a similar interval, similar to that in which TAS has been localized (Parvari et al., 1994).

The intense interest in the Fragile X syndrome and the FMR1 gene in Xq27.3 has continued to promote a variety of probing studies. Eichler et al. (1994) have analyzed the instability in the gene determined by the length of uninterrupted CGG repeats; and Kunst and Warren (1994) have noted that cryptic and polar variation of the repeat could result in predisposing normal alleles. Hirst et al. (1994), Snow et al. (1994), and Arinami et al. (1993) have also analyzed sequences in the repeat region of unrelated individuals and family members to determine possible origins of the fragile X triplet repeat expansion. Additional variations in the origin and fate of altered FMR1 genes have been noted. They include two cases of FMR1 deletion associated with mental impairment (Hirst et al., 1995). An instance of apparent gene conversion leading to loss of mutation at the locus has also been noted (van den Ouweland et al., 1994a). Brown et al. (abst. S11) use a general method to identify an Alu SSCP polymorphism in the FMR1 gene, as a potential aid to linkage disequilibrium studies.

Clinical analyses of correlates of triplet expansion and phenotype have been extended by two studies (Abrams et al., 1994; Rousseau et al., 1994a). Linkage to infantile autism was excluded by linkage tests (Hallmayer et al., 1994).

More mechanistic studies have indicated that triplet expansion may promote the methylation of the CpG island of the FMR-1 gene (Luo et al., 1993) and that one mentally normal male carrier of a fragile X full mutation had a "methylation mosaic" pattern, with a premutation and 40% abnormal methylation at the standard FMR-1 restriction site; and Shapiro et al (1994) report asymmetric methylation with full mutation in two complex mosaic females associated with normal intellect. Iida et al. (1994) further point out that the FMR1 gene is differently methylated in various embryonic tissues, which could affect both prenatal diagnosis and penetrance. To aid in studies of pathophysiology, an *Fmr1* knockout mouse has been obtained which shows macroorchidism and some evidence of mental retardation (Dutch-Belgian Fragile X Consortium, 1994).

Further distal in Xq27.3–q28 are FRAXE and FRAXF. The expanded GCC repeat of FRAXE has been seen in affected males and females (Hamel et al., 1994; Knight et al., 1994), with the suggestion of possible candidate transcripts for a disease gene encoded in a region deleted between DXS296 and DXS295 in two patients (Gedeon et al., 1995 and abst. S4). Brown et al. (abst. S12) report a microdeletion associated with a complex mosaic-FRAXA mutation.

FRAXF shows still a third GCC repeat expansion, methylation and unstable sequences in 5 individuals with normal repeat lengths at FRAXA and FRAXE (Parrish et al., 1994; Knight et al., 1994); the locus falls between IDS and GABRA3.

IDS has been shown to be often caused by inversion of the IDS gene resulting from recombination with IDS-related sequences (Bondeson et al., 1995). Correlation of mutations and phenotypes for missense changes in the gene have been examined by Jonsson et al. (1995).

The myotubular myopathy gene MTM1 has been assigned to a 600-kb region between DXS304 and DXS497 (Dahl et al., 1995).

A fascinating group of genes, the melanoma antigen gene (MAGE) family includes 12 members. At least one member had been mapped to Xq28 (see Chen et al., 1994; Wang et al., 1994b; Oaks et al., 1994). Poustka et al. (S5) and Parrish et al. (S6) now find that all 12 members of the family fall into a 3.5-Mb region of Xq28, clustered in 3 map intervals. They are indicated by labeled blocks on the map, along with relative locations of four definitively placed members of the family.

Additional studies of previously reported genes in the very gene-rich region between DXS52 and the RCP/GCP locus have been reported. They include the L1CAM gene involved in hydrocephalus, SPG1, and MASA syndrome (Fransen et al., 1994; Jouet et al., 1994; Vits et al., 1994); the adrenoleukodystrophy gene (Sarde et al., 1994; Braun et al., 1995); the RENBP gene (van den Ouweland et al., 1994b); another gene (DXS1357E) adjacent to the ALD gene (Mosser et al, 1994); HCFC1 (Frattini et al, 1994; Wilson et al., 1995); and AVPR2 (Wildin et al., 1994; Bichet et al., 1994); Wenkert et al., 1994). In one further study of nephrogenic diabetes insipidus, X-linked dominant inheritance was unexpectedly observed with an AVPR2 gene that is structurally normal (Friedman et al., 1994). Among the new genes reported in this region by Tibioli et al. (1994) is a human homologue of the ARD1 N-acetyl transferase of Saccharomyces cerevisiae. Another new gene, first detected in the syntenically equivalent portion of the mouse X chromosome, is a methyl CpG binding protein, *Mecp2* (Quaderi et al., 1994). A creatine transporter gene in the region (SLC6A8; Nash et al., 1994) has also been cloned and characterized. Eichler et al. (abst. S8) report that duplication of this gene recently during evolution has accompanied its transfer to 16p11, and also demonstrate a location adjacent to CDM, ALD, and DXS1357E (see below for larger-scale sequencing and gene localization in this region).

At the RCP/GCP locus, heterogeneity of pigment genes and inherited variation in human vision has been analyzed in further detail, with the realization that the number of pigment genes can be more variable than previously known (Nathans, 1994; Neitz and Neitz, 1995; Hunt et al., 1995). Comparative analysis has also been extended with studies of the pigments

in great apes compared to humans (Deeb et al., 1994; cf. review in Tovee et al., 1994).

In the distal, still highly gene-rich region between RCP/GCP and G6PD, the gene responsible for Emery-Dreifuss muscular dystrophy has been identified (emerin; Bione et al., 1994). QM, a novel c-Jun associated transcription factor (Farmer et al., 1994), and a rab GDP-dissociation inhibitor (GDI or XAP-4; Sedlacek et al., 1994; Bachner et al., 1995)) have been further studied.

Distal to G6PD, a number of genes have been mapped to various extents. TXREB pseudogene and MPP1 (Das and Gitschier, 1994) lie between G6PD and Factor VIII.

Concerning Hemophilia A, more Factor VIII gene rearrangements have been noted (Goodeve et al., 1994; Jenkins et al., 1994). In one extraordinary instance (Murru et al., 1994), a DNA fragment from Xq21 replaced a deleted region that spans the entire Factor VIII gene. Rossiter et al. (1994) have shown that inversions causing severe Hemophilia A arise almost exclusively in male germ cells.

For Hemophilia A, as in the case of Fragile X syndrome, the disease now has a mouse model, made by disrupting the factor VIII gene (Bi et al., 1995) and is also being studied in sheep (Backfisch et al., 1994).

Distal to Factor VIII lie at least two disease genes. One, MTCP1, was identified from an Xq28 translocation to the T cell receptor alpha locus, and is a candidate gene potentially involved in leukemogenesis (Stern et al., 1993; Fisch et al., 1993; Thick et al., 1992).

Exchanges between Xq and Yq in the Xq28 region, possibly facilitated by interactions of Xq/Yq pseudoautosomal region DNA (Kvalfy and Brown, 1994) can lead to supernormal X- linked gene expression in severely retarded males with 46,XYq– karyotype, due to failure of inactivation of the translocated Xq genes (Lahn et al., 1994).

Global/regional gene searches

Standard techniques like direct selection are continuing (see general discussion above and, e.g., Lawrence et al., 1994 and abst. A3, particularly for work in Xq27.3–q28). To these have been added the renewed use of microclone probes generated by laser microdissection (Yokoi et al., 1994).

Perhaps the most successful approaches for functional analysis are based on different ways to recover fragments sure to be parts of genes. The 5th X chromosome workshop reviewed the ongoing use of rare-cutter restriction mapping and CpG island subcloning as region-specific approaches, thus far particularly for Xq28. A complementary approach is the assignment to a region of ESTs from the systematic efforts to develop them from cloned cDNAs (see, for example, Wehnert et al., abst. A4). The EST assignment gains increased power by linking it to YAC contigs (Mazzarella and Srivastava, 1994) and to further cosmid contig construction based on YAC contigs (Parrish et al., abst. S6), which helps to construct bacterial clone coverage of a region while the map position of cDNAs is refined.

An interesting method combines features of both approaches (subcloning and EST assignment) to harvest a portion of the transcribed sequences in a region. As exemplified in abst. S11 (Esposito et al.), STSs developed from a region are tested against cDNA libraries (or by RT-PCR against cellular RNA preparations), and are found to include many ESTs; 40% of the STSs in Xq28 were thus found to represent transcribed sequences.

Genes and candidate genes from long-range sequencing

Although still limited by cost, the direct sequencing of a region of DNA is the most certain way route to a complete catalogue of encoded genes and potential genes, and will increasingly become the method of choice (see discussion in Chen et al., 1994). Extensive pilot testing of gene prediction/recovery by direct sequencing compared to the variety of other methods in use has now been initiated by the consortium of groups tackling substantial regions of Xq28.

Relevant reports were given at the workshop from several groups (abst. A5, S7, S9, and S10). Andersson et al. (abst. A5) have focused on cosmid sequencing, increasing the efficiency of the random shotgun approach. They have completed the sequence of 20 cosmids, including 13 from the FRAXA to IDS region and 4 outside of the region. This includes long contiguous regions of at FMR1 (152 kb) and IDS (130 kb) (see Table I for accession numbers).

Sequencing is now essentially complete in a 570 kb stretch high in GC and gene content, although these sequences are as yet not present in publicly accessible databases, and are therefore not represented in Table I. Platzer et al. (abst. S7) summarize the contents of 360 kb of DNA around L1CAM and extending through the color vision locus. Thirteen confirmed genes and at least 3 more putative genes (based on computer-assisted predictions) have been placed. Thus, the gene complement seems to reach 16–17, or on the order of 1/20 kb, confirming the predicted high gene content. The clearly identified genes (and one pseudogene) include SLC6A8, CDM, ALD, an isocitrate dehydrogenase and a serine kinase, translocon associated protein, delta subunit (TRAP), a cytochrome C pseudogene, L1CAM, AVPR2, TE2, RNBP, transcription factor HCF1, and a methyl-CpG- binding protein (MeCP2) (note that some of these are also discussed in the text on single gene studies above). In addition, there are three putative genes predicted. One of those, called C1, has been independently isolated as a proven gene, with homology with rho-GAP signaling proteins (Bione et al., abst. S14).

Comparable analysis has been applied and extended in 220 kb of high GC DNA between the RCP/GCP and G6PD loci (abst. S9 and S10). D'Urso et al. (abst. S9) report a 12 kb inverted repeat with 99.2% sequence identity and subregions of >80% GC that complicated the analysis. The region contains very abundant Alu's and half-Alu's, but only a limited repertoire of MERs and no L1 sequences at all. It is >90% transcribed (Chen et al., abst. S10), with a total of 17–

Table I. Sequence database entries for genomic DNAs greater than 15 kb and derived from the X chromosome obtained from the Genome Sequence Data Base July 18, 1995. (total = 847,616 bp)

Entry name[a]	Accession number	Length in base pairs	Position on consensus map	Name as obtained from data base entry
HUMFMR1S	L29074	152,351	q27.3	Homo sapiens fragile X mental retardation protein (FMR-1) gene
HUMIDUR	L43581	130,000	q28	Homo sapiens iduronate-2-sulfate sulfatase (IDS) gene, 5' region and pseudogene
HUMFGLBTK	L35265	69,363	q22.1	Human ftp-3 gene, exon 1; alpha-D-galactosidase A (GLA) gene, and flanks
HUMHPRTB	M26434	56,737	q26.1	Human hypoxanthine phosphoribosyltransferase (HPRT) gene, complete cds
HSG6PDGEN	X55448	52,173	q28	Homo sapiens G6PD gene for glucose-6-phosphate dehydrogenase
HUM1193DXS	L39643	41,183	q27.3	Homo sapiens chromosome X cosmid insert including markers DXS1193, UT587
HUMDYSTROP	M86524	38,770	p21.1	Human dystrophin gene
HUMDXS455A	L31948	38,409	q28	Human cosmid insert containing polymorphic marker DXS455
HUMFIXG	K02402	38,059	q26.3	Human factor IX gene, complete cds
HS14B7	Z49258	36,429	q28	Human DNA sequence from cosmid 14B7 in Xq28 with transketolase pseudogene
HSU09822[b]	U09822	34,683	–	Human cosmid clone 26h7 from Xq27.2-q27.3
HUMREPSTS	L40416	33,450	q27.3	Homo sapiens DNA repeat regions (DXS1215)
HUMRTMD	L08092	32,000	p21.1	Homo sapiens dystrophin (DMD) gene, intron 7, transposon-like sequence
HSCG1160	Z46936	28,230	q28	Human cosmid cG1160 from Xq28 containing 3' end of green opsin gene
HSHCF1	X79198	17,760	q28	Homo sapiens HCF-1 gene
HUMXIST	M97168	16,481	q13.2	Homo sapiens X (inactive)-specific transcript (XIST) complete exon
HSNCAMX1	Z29373	16,288	q28	Homo sapiens gene for neural cell adhesion molecule L1
HSQLL2C9[b]	Z47046	15,250	–	Human cosmid QLL2C9 from Xq28

[a] These are listed in descending order of length.

[b] These entries were not positioned on the consensus map (Fig. 1) due to the absence of information regarding marker content. Precise position of the clones sequenced for these two could not be determined from the database entry, although each has a rough position from its description. All other entries can be found in the position indicated on the consensus map.

21 CpG islands. (The activity in this region has been intense, and several genes have been studied by more than one group; see Table II with the various names associated with genes/loci.) Among a group of 21 predicted gene candidates (that is, roughly 1 gene/10 kb), 12 are coincident with reported cDNAs in the region, and a thirteenth was already known to be in distal Xq. Two of these, sex (6.3) and G4.8 (the DNase I-like protein) have been sequenced from full-length cDNAs (abst. S14). Since GRAIL predicted exons in those 13 genes with 92–95% accuracy, the other 8 putative genes have a strong probability of being real. Consistent with this expectation, primer pairs derived from predicted exons have thus far found cognate signals for 4 of the 8 putative genes in cDNA collections. In an interesting example of the

Table II. Genes definitively demonstrated in the 220-kb region between RCP/GCP and G6PD (centromeric to telomeric)

	Gene[a]	Sequence database accession numbers
1.	RCP/GCP)	M13300–M13305, K03490–K03497, M13306
2.	FLN1	X53416
3.	EMD (alias emerin and STA)	X82434
4.	QM	M73791
5.	DNL1L	L40823
	XAP–1	X74606
	G4.8	X87196
6.	XAP–2	X74607
	G4.5	X87198
7.	Vacuolar H–ATPase	D16469
	XAP–3	X74605
	16A	X87195
8.	GDI	D45021
	XAP–4	X74608
	1A	X87194
9.	XAP–5	X74611
	9F	X87199
10.	c–met proto–oncogene like and c–sea like protein, (sex)	
	XAP–6	X74609,
	6.3	X87197
11.	GdX	J03589
12.	P3	X12458
13.	2–19	X87193
	XAP–7	X74610
14.	G6PD	X55448

[a] Official names, lab designations and aliases are provided for 14 genes resident in a ~220 kb spanning from the color vision gene cluster to G6PD.

use of combined genomic and cDNA sequences, Parrish et al. have completed the cDNA sequence and defined the exon-intron borders in the DNL1L gene based on genomic sequence provided by Chen and coworkers (Parrish et al., 1995).

With this long contiguous region sequenced, comparative studies begin to take on cumulative force. In addition to the findings of a region that is duplicated at subtelomeric sites of other chromosomes (see above), comparative analyses have also begun with homologs in the pufferfish. G6PD and L1CAM have thus far been compared. Exon/intron structures are essentially identical in the two species, and comparable tissue-specific splicing is seen for L1CAM. The L1CAM gene is about the same size in both (Nyakatural et al., abst. P4), but smaller introns make the fish G6PD only about 1/4 the size of its human counterpart (Mason et al., 1995). The results are consistent with a striking unity of biochemistry.

General mapping

Several abstracts presented data regarding "whole chromosome" approaches to the X map. Two concern primarily YAC-based mapping (abst. A1 and A2). Nagaraja et al. (abst. A1) estimate 70% completion of the map based on the number of STSs developed (2100) and have used these to identify close to 4500 YACs across the chromosome. Ross et al. (abst. A2) have also taken a chromosome-wide, YAC-based approach to mapping, making extensive use of YAC:YAC hybridization, fingerprinting and Alu PCR to define and confirm contigs. Thirty contigs currently comprise 70% of the chromosome (45 Mb of the short arm and 64 Mb of the long arm). FISH localization has assisted in regional positioning of clones and contigs. Whole genome radiation hybrids are being used by Lehrach and co-workers (abst. A6 and A8) to confirm and refine marker order across the chromosome. Deviation from the order provided by the consensus map of XCW5 was minimal with the first 50 markers. The radiation hybrid map has been helpful with YAC contig efforts.

Whole chromosome approaches to gene identification and assignment are discussed in three abstracts (abst. A3, A4 and A7). Korn et al. (abst. A3) have developed materials for identifying genes expressed from the X chromosome. These include Not I linking libraries which have been used to select cDNAs from several cDNA libraries. Wehnert et al. (abst. A4) described the further use of "reciprocal probing" to develop paired genomic and cDNA materials from the X chromosome. They have regionally assigned more than 100 cDNAs derived from heart and placental libraries. Gianfancesco et al. (abst. A7) describe regional assignment of 60 ESTs derived from the IMAGE consortium normalized infant brain library using 13 somatic cell hybrids which divide the chromosome into 40 intervals.

No data were presented regarding whole chromosome efforts to refine the genetic map of the chromosome. Every effort was made by the editors to include relevant polymorphic markers in the consensus physical map in Fig. 1, however some additional data are expected with the next release of the CEPH/Genethon whole genome genetic map. The 2D map described by Fain et al. (Fain et al. 1995) has been used in construction of the consensus map and is referred to in the individual sections described above. The density of highly polymorphic markers across the chromosome is very high on average, with a few thin spots. These will doubtless be filled in the coming year. The remaining task for the genetic map will be development of order and distance data at high odds across the chromosome using the CEPH and CHLC data.

Sequencing Prospects

An ad hoc meeting at Cold Spring Harbor had discussed some projected sequencing plans, in order to anticipate possible scenarios and try to coordinate activities. The discussion was continued at the X chromosome workshop. The goals were to accommodate both larger- and smaller-scale projects with a flexible plan that will also be responsive to decisions by various funding agencies. Three types of discussions were included: Guidelines for participation in a consortium approach; targets of various groups for the coming year; and possible contributions to the materials for sequencing.

Guidelines for participation

The general notion was to build on existing international consortium schemes, such as those that have initiated the analysis of Xq28, yeast, etc., maximizing efficiency and minimizing duplication of effort. After some discussion, consensus was reached on the following rules of thumb:

1.) Sequencing of at least 95% of the chromosome was judged feasible. Sequencing would be complete, base-by-base, defined by at least 99.9% accuracy and few if any gaps. Some toleration was suggested for regions in which repetitive sequences occur in tandem (some uncertainty in the number of A's at the end of an Alu, etc.), and groups would be free to carry out sequencing by any of a number of means — that is, with alternate types of clones, strategies, initial concentration on potential transcription units, etc. — but a yearly work allocation would have to be completed before another allocation were started.

2.) Each participating group could sign up for an amount of activity that would require a minimum commitment, based on proven previous performance.

3.) If a group could not fulfill its allotment of work (for example, if funding fails), there is an automatic return of that portion of the overall effort to the general pool to be taken up by other groups.

4.) The sequence obtained would be provided to the community on the basis of the assembly from raw data files of stretches longer than 1 kb, by deposition at freely available ftp sites. Shorter units of large clones would be replaced by larger ones as assembly proceeded. Units that reached "completion" (that is, were finished at the cosmid/BAC/YAC level) would be at least roughly annotated and deposited in Genbank. It was expected that cDNAs/ESTs and STSs across the chromosome would be filled in, and that the annotation would be updated and progressively improved; but neither a fixed group of analyses for the annotation nor a mechanism for updating were discussed.

5.) There was some expectation that the sequenced regions would be integrated into some graphic database representation, probably building on a version of ACEDB; but this was not explored in detail.

Participation by groups in the next year

At present, the community is operating on the basis of a distribution of effort worked out at the last X chromosome workshop. A group of European laboratories have proposed a continuation of the previous allocations to finish Xq28. The projections are included in the following summary as the work to be done in the next year(s).

1.) Group of M. D'Urso in Naples. Has participated in doing about 260 kb of sequencing moving telomeric from the color vision locus in conjunction with E. Chen. Will continue sequencing to the Xq telomere, about 1.8 Mb, over a period of 2–3 years.

2.) Group of A. Rosenthal. Would like to finish 3 Mb of Xq28 in the GABRA- L1CAM region by April 1, 1996

3.) Group at the Baylor Center. Richard Gibbs' group has sequenced some scattered cosmids (for example, 69 kb surrounding BTK in Xq22) and about half of 2 Mb including the Fragile X locus and moving telomeric into Xq28. This includes long contiguous regions of at FMR1 (152 kb) and IDS (130 kb). In the coming year, his group would expect to finish the 2 Mb and take on about another 2 Mb of additional X DNA (location not yet clear).

4.) Group at ABD/Washington University Genome Center. The group is currently funded to do 1–2 Mb of sequencing for each of the next three years. As discussed at the last X chromosome workshop, the group has continued to complete the assigned 220 kb in Xq28, to analyze a 150-kb test YAC in Xq25, and to work on the sequencing of about 1 Mb of Xq26 and a test region of Xq13 by June, 1996.

5.) Groups at the Sanger Centre and Washington University Sequencing Center. The groups are now operating at a throughput capacity of more than 10 Mb/year, primarily on the nematode genome. The Cambridge unit has done about half of a proposed 2 Mb on chromosome 4, some of the 360 kb in Xq28 that also includes the completed work of Rosenthal's group, and will be sequencing the region between the Baylor and Rosenthal allotments (on the order of 2 Mb) to help complete Xq28 in the coming year. In addition this group is currently sequencing several megabases in Xq22 and assembling sequence-ready maps in regions of Xq25 and Xq26–q27.

The Washington University Sequencing Center has begun pilot work on a region of Xp22 in which both YACs and cosmids show unusually high quality. They are focusing first on the region containing the HYP gene, and will carry that forward at a level of several hundred kb for the next year.

6.) Other groups involved? At the X Workshop, several groups expressed interest, and there were indications that an allocation system would be required. Even in Xq28 there has been some overlap of activities, and at the Workshop both the Sequencing Center at Washington University and the Berlin group of Hans Lehrach discussed sequencing in the HYP region. The scale of work beyond 1996 in various groups remained to be decided, because larger-scale programs will be dependent on the decisions of funding agencies. However, the

composition of the X and the suggested rules for the Consortium approach would favor a reasonable accommodation of the needs of various groups. This is because Xq28, which is being finished early on, is the only extensive highly gene-rich region on the X; and the projected very rapid deposit of sequenced regions for the entire community will tend to minimize efforts to choose regions for privileged hunts for disease genes, etc.

Sequencing substrates and map backup

The upfront provision of clones and materials for sequencing was discussed at some length. The Consortium YAC collection (see Introduction) would provide a backup and first line coverage of the chromosome. There was further discussion about optimal starting materials for sequencing. To date, approaches using either YAC or bacterial clones (mostly cosmids, but also P1s, PACs or BACs) have been adopted. An emerging consensus is that bacterial clones may be the preferred starting material in view of the known chimaerism and instability of YACs, particularly in defined regions of the chromosome. However, this choice is subject to the availability of mapped bacterial clone contigs, and YACs could still help to provide DNA from gaps in bacterial clone contigs. The existing clone resources include the Livermore gridded flow-sorted X chromosome cosmid library of P. de Jong (6 complexities) and a library constructed at the Los Alamos laboratories (not yet picked). The ICRF flow-sorted cosmid library (4 complexities gridded) and Xq24–q28 specific cosmid library (from A.-M. Poustka and S. Tsuji) have also been used. The X-chromosome specific resources are now complemented by total genomic libraries in BACs and PACs.

In the coming year, additional clone resources will be forthcoming, possibly including YACs with lower chimaerism levels, and several groups are actively binning cosmids and other clones across defined stretches of the chromosome. The aim is to be able to provide adequate upfront sequencing substrates for the entire chromosome by the time that longer-range extensive sequencing projects are ready for them. By that time, it would also be necessary to work out a way to define the allocation of chromosomal regions and to integrate sequencing activities.

Comparative Mapping and Sequencing

Status of mouse X map

Over 500 loci, both genic and microsatellite, have now been mapped genetically on the mouse X chromosome (see X Chromosome Committee report - Mammalian Genome Vol. 6 – to be published). A number of microsatellites have been mapped to high resolution on the European Backcross facility providing a high resolution genetic map that underpins the construction of a high integrity physical map (Quaderi et al. abst. P1)

Over 400 YACs have been recovered to available STSs (Boyd et al. abst. P2; Herman et al. abst. P3; Quaderi et al. abst. P1). A large number of small contigs have been identified and several large contigs spanning 3–5 Mb have been established. In particular, a contig of 5 Mb stretching from *Ids* (IDS) to *Cf8* (F8) with one small gap distal to *G6pd* (G6PD) has been built (Herman et al. abst. P3).

Evolutionary Breakpoints

There remain eight conserved linkage groups between the mouse and human X chromosomes. However, there has been further characterization of the conserved linkage boundaries in proximal Xp which are now defined as:

DXF34//ALAS2 – DXS1272E//NPHL – WASP//PFC – XK//DMD

In addition, there has been a recent report (Rugarli et al. abst. P7) describing differing map locations for the *Clcn4* gene amongst mouse species. On the *Mus spretus* X chromosome, *Clcn4* maps close to the pseudoautosomal region but in laboratory inbred strains maps to proximal mouse chromosome 7. This suggests that the pseudoautosomal boundary is continuing to move in recent evolutionary time.

Evolution of the X chromosome

Comparative mapping for more distant groups e.g. marsupials has revealed to a first order approximation that the original ancestral X extends from GATA1 at Xp11.23 to Xqter, with other Xp markers being autosomal in marsupials (Wakefield and Graves; abst. P6). A possible relationship between intrachromosomal rearrangements and speciation is indicated by the work of Rugarli et al. (see above). The phenotype of intersexual marsupials suggests that there are hitherto unrecognized homeobox genes concerned with mammary gland development on the original X (Cooper et al. abst. P5). A report on the Fugu fish L1CAM gene sequence initiates comparison of X chromosome sequences across one of the widest evolutionary distances in extant vertebrates (Nyakatura et al. abst. P4) and surprisingly demonstrates that the Fugu gene is similar in size to the human gene. Comparative mapping could be assisted by the inclusion on zoo blots of DNA samples from representatives of all major groups and by the identification of further conserved ESTs.

Participants

Björn P. Andersson
Department of Molecular and Human Genetics
Baylor College of Medicine
One Baylor Plaza
Houston TX 77030
USA
Tel: 1-713-798-6539
Fax: 1-713-798 6521
bjorna@bcm.tmc.edu

Andrea Ballabio
TIGEM
Via Olgettina 58
20132 Milano
ITALY
Tel: 39-2-21560206
fax: 39-2-21560220
ballaba@dibit.hsr.it

N. Torben Bech-Hansen
Department of Paediatrics
Alberta Children's Hospital
1820 Richmond Rd. S.W.
Calgary, Alberta T2T 5C7
CANADA
Tel: 1-403-229-7243
Fax: 1-403-229-7624
ntbech@acs.ucalgary.ca

David Bentley
The Sanger Centre
Hinxton Hall
Hinxton, Cambridge
CB10 1RQ
UK
Tel: 44-223-494947
fax: 44-223-494919
drb@sanger.ac.uk

Silvia Bione
Istituto di Genetica Biochimica ed Evoluzionistica
CNR
Via Abbiategrasso 207
27100 Pavia
ITALY
Tel: 39-382-546341
Fax: 39-382-422286
bione@ipvgbe.igbe.pv.cnr.it

Kym Boycott
Department of Paediatrics
Alberta Children's Hospital
1820 Richmond Rd. S.W.
Calgary, Alberta T2T 5C7
CANADA
Tel: 403-229-7211 xt5679
Fax: 403-229-7264
kboycott@acs.ucalgary.ca

Yvonne Boyd
MRC Radiobiology Unit
Chilton
Harwell, Didcot
Oxon OX11 0RD
UK
Tel: 44-235-834-4393
Fax: 44-235-834-776
y.boyd@har-rbu.mrc.ac.uk

Steve D.M. Brown
Department of Biochemistry and Molecular Genetics
St. Mary's Hospital Medical School
Norfolk Place, Paddington
London W2 1PG
UK
Tel: 44-71-723-1252 Ext. 5484
Fax: 44-71-706-3272
s.brown@sm.ic.ac.uk

Ted Brown
Department of Human Genetics
NYS Institute for Basic Research
Staten Island, NY 10324
USA
Tel: 1-718-494-5363
fax: 1-718-494-1026
WTBIBR@aol.com

Jianhua Chai
Human Genome Laboratory
Institute of Genetics
Fudan University
Shanghai 200433
CHINA
Tel: 86-21-549-2222 x4101
Fax: 86-21-549-0323
jhchai@fudan.ihep.ac.cn

Aarti Chand
Department of Biochemistry
University of Oxford
South Parks Road,
Oxford, OXI 3QU,
UK
Tel: 44-865-275314
Fax: 44-865-275318
achand@bioch.ox.ac.uk

Ellson Chen
Applied Biosytem Division
Perkin-Elmer Corp.
850 Lincoln Centre Drive
Foster City CA 94404
USA
Tel: 1-415-638-5107
Fax: 1-415-572-2743
ChenEY@ccmail.apldbio.com

Alfredo Ciccodicola
Istituto Internazionale di Genetica e Biofisica
Via Guglielmo Marconi
12 - 80125 Napoli
ITALY
Tel: 39 81 7257 250
Fax: 39 81 593 6123
stb@iigbna.iigb.na.cnr.it

Alison Coffey
The Sanger Centre
Hinxton Hall
Hinxton, Cambridge
CB10 1RQ
UK
Tel: 44-223-494946
Fax: 44-223-494919
ajc@sanger.ac.uk

Desmond W. Cooper
School of Biological Sciences
Macquarie University
School of Biological Sciences
Sydney, NSW 2109
AUSTRALIA
Tel: 61-2-805-8214
Fax: 61-2-805 8245
dcooper@rna.bio.mq.edu.au

Bob Cottingham
BCM Human Genome Center
Department of Molecular and Human Genetics, Room S903
One Baylor Plaza
Baylor College of Medicine
Houston, Texas 77030
USA
Tel: 1-713-798-4275
Fax: 1-713-798-5386
bwc@bcm.tmc.edu

Frans P.M. Cremers
University Hospital Nijmegen
417 Department of Human Genetics
Geert Grooteplein 20
P.O. Box 9101
6500 HB Nijmegen
THE NETHERLANDS
Tel: 31 80 614017
Fax: 31 80 540488
h.ropers@antrg.azn.nl

Jonathon Derry
Immunex R & D Corp
51 University St.
Seattle WA 98101
USA
Tel: 206 587 0430
Fax: 206 233 9733
jderry@immunex.com

Michele D'Urso
Istituto Internazionale di Genetica e Biofisica
Via Guglielmo Marconi
12 - 80125 Napoli
ITALY
Tel: 39 81 7257 247
Fax: 39 81 7257 247
durso@iigbna.iigb.na.cnr.it

Evan Eichler
BCM Human Genome Center
Department of Molecular and Human
Genetics, Room 902E
One Baylor Plaza
Baylor College of Medicine
Houston, Texas 77030 USA
Tel: 1-713-798-3122
Fax: 1-713-798-5386
eeichler@bcm.tmc.edu

Giovanni Ferrero
Department of Molecular and Human
Genetics
Baylor College of Medicine
One Baylor Plaza
Houston TX 77030
USA
Tel: 1-713-798-5480
Fax: 1-713-798-5386
gferrero@bcm.tmc.edu

Michel Fontés
INSERM U406
Faculte de Medecine de la Timone
BP24
13351 Marseille Cedex 5
FRANCE
Tel: 33 91 78 44 77
fax: 33 91 80 43 19
fontes@lgpd.univ-mrs.fr

Fiona Francis
Max-Planck-Institut fur Molekulare Genetik
Ihnestraszlige 73
14195 Berlin
GERMANY
Tel: 49 30 8413 1612
Fax: 49 30 8413 1380
francis@mpimg-berlin-dahlem.mpg.de

Brunella Franco
TIGEM
Via Olgettina 58
20132 Milano
ITALY
Tel: 39-2-21560202
Fax: 39-2-21560220
franco@andromeda.hsr.it

Andreas Gal
Institut für Humangenetik
Universität-Krankenhaus Eppendorf
Butenfeld 32, D-22529 Hamburg
GERMANY
Tel: 49 40 4717 2120
Fax: 49 40 4717 5138

Jozef Gecz
Department of Cytogenetics and Molecular
Genetics
Women's and Children's Hospital
75 King William Road
SA5006 North Adelaide
AUSTRALIA
Tel: 1-618-204-7023
Fax: 1-618-20407342
jgecz@medicine.adelaide.edu.au

Nicola Goddard
Department of Human Genetics
Ridley Building
University of Newcastle upon Tyne
Newcastle upon Tyne, NE1 7RU
UK
Tel: 44-191-222-6829
Fax: 44-191-222-6662
n.j.goddard@ncl.ac.uk

Gerd Haberhausen
Institut fur Humangenetik
Schlangenzahl 14
D-35392 Giessen
GERMANY
Tel: 49 641 702 4147
Fax: 49 641 702 4158
Gerd.Haberhausen@humangenetik.med.uni-giessen.de

André Hanauer
I.G.B.M.C., Pare d'Innovation
1, rue Laurent Fries
67404 Ilkirch Cedex
FRANCE
Tel: 33 88 65 34 00
Fax: 33 88 65 32 46
andre@titus.u-strasbg.fr

Alison Hardcastle
Department of Molecular Genetics
Institute of Ophthalmology
Bath Street
London EC1V 9EL
UK
Tel: 44 71 608 6915
Fax: 44 71 608 6863
ahardcas@hgmp.mrc.ac.uk

Gail E. Herman
Department of Molecular and Human
Genetics, T821
Baylor College of Medicine
One Baylor Plaza
Houston TX 77030
USA
Tel: 1-713-798-6526
Fax: 1-713-798-5386
gherman@bcm.tmc.edu

Shirin Joseph
The Sanger Centre
Hinxton Hall
Hinxton, Cambridge
CB10 1RQ
UK
Tel: 44 223 494843
Fax: 44 223 494919
shirin@sanger.ac.uk

Bernhard Korn
Molekulare Genomanalyse
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
GERMANY
Tel: 49 6221-423416
Fax: 49 6221 423454
b.korn@dkfz-heidelberg.de

Johan Kumlien
Genome Analysis Laboratory
Imperial Cancer Research Fund
P.O. Box 123, Lincoln's Inn Fields
London WC2A 3PX
UK
Tel: 44 71 269 3296
Fax: 44 71 269 3068
kumlien@icrf.icnet.uk

Hans Lehrach
Max-Planck Institut fur Molekulare Genetik
Ihnestraße 73
D-14195 Dahlem
Berlin
GERMANY
Tel: 49 30 8413 1221
Fax: 49 30 8413 1380
huntt@icrf.icnet.uk

Bronwen Loder
HUGO Europe
Cambridge University
Department of Pathology
Tennis Court Road
Cambridge CB2 1QP
UK
Tel: 44-223-339398
Fax: 44-223-339398
hugo@mole.bio.cam.ac.uk

Sandra MacMillan
Department of Molecular Microbiology and
Center for Genetics in Medicine
Washington University School of Medicine,
Box 8230
660 S. Euclid Ave.
St. Louis, MO 63110 USA
Tel: 1-314-362-2760
Fax: 1-314-362-3203
sandra@genetics.wustl.edu

Thomas Meitinger
Ludwig-Maximilians-Universität
Goethestrasse 29
D-80336 Munchen
GERMANY
Tel: 49 89 5160 4466
Fax: 49 89 5160 4780
thomas@pedgen.med.uni-muenchen.de

Andy Miller
Case Western Reserve University
School of Medicine
Department of Genetics
10900 Euclid Ave.
Cleveland OH 44106-4955
USA
Tel: 1-216-368-3327
Fax: 1-216-368-3432
apm6@po.cwru.edu

Tony Monaco
Imperial Cancer Research Fund
Institute of Molecular Medicine
John Radcliffe Hospital
Headington
Oxford OX3 9DU
UK
Tel: 44-865-222-371
Fax: 44-865-222-431
a_monaco@icrf.icnet.uk

Steven Mumm
Department of Molecular Microbiology and
Center for Genetics in Medicine
Washington University School of Medicine,
Box 8230
660 S. Euclid Ave.
St. Louis, MO 63110
USA
Tel: 1-314-362-2760
Fax: 1-314-362-3203
stevem@borcim.wustl.edu

Ramaiah Nagaraja
Department of Molecular Microbiology and
Center for Genetics in Medicine
Washington University School of Medicine,
Box 8230
660 S. Euclid Ave.
St. Louis, MO 63110
USA
Tel: 1-314-362-2760/2191
Fax: 1-314-362-3203
nagaraja@borcim.wustl.edu

David Nelson
BCM Human Genome Center
Department of Molecular and Human
Genetics, Room 902E
One Baylor Plaza
Baylor College of Medicine
Houston, Texas 77030
USA
Tel: 1-713-798-4787
Fax: 1-713-798-6370 or -5386
nelson@bcm.tmc.edu

Ulrike Orth
Institut für Humangenetik
Medizinische Universitat zu Lübeck
Ratzeburger Allee 160
D-23538 Lübeck
GERMANY
Tel: 49-451-500-2622
Fax: 49-451-500-4187

Julia Parrish
Department of Molecular and Human
Genetics
Baylor College of Medicine
One Baylor Plaza
Houston, Texas 77030
USA
Tel: 1-713-798-7898
Fax: 1-713-798-5386
jparrish@bcm.tmc.edu

Matthias Platzer
Institute of Molecular Biotechnology
Beutenbergstrasse 11
D-07745 Jena
GERMANY
Tel: 49-3641-656245
Fax: 49-3641-656255
mplatzer@imb-jena.de

Chris Porter
Genome Data Base
The Johns Hopkins University School of
Medicine
2024 East Monument Street
Baltimore MD 21205-2100
USA
Tel: 1-410-614-1851
Fax: 1-410-614-0434
cporter@gdb.org

Annemarie Poustka
Molekular Genomanalyse
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
GERMANY
Tel: 49 6221-424742
Fax: 49 6221-423454
g.haberhauer@dkfz-heidelberg.de

Gudrun Rappold
Institut für Humangenetik und Anthropologie
Universität Heidelberg
Im Neuenheimer Feld 328
D-69120 Heidelberg
Tel: 49 6221-563890-3897
Fax: 49 6221-565332
christine.fischer@urz.uni-heidelberg.de

Hugues Roest-Crollius
Max-Planck-Institut für Molekulare Genetik
Ihnestraße 73
14195 Berlin
GERMANY
Tel: 49 30 8413 1612
Fax: 49 30 8413 1380
roest@mpimg-berlin-dahlem.mpg.de

Mark Ross
The Sanger Centre
Hinxton Hall
Hinxton, Cambridge
CB10 1RQ
UK
Tel: 44 223 494919
Fax: 44 223 494839
mtr@sanger.ac.uk

Peter S.N. Rowe
University College London
Middlesex Hopital
Department of Medicine
Mortimer St.
London W1N 8AA
UK
Tel: 44-71-636-8333 x3261
Fax: 44-71-636-3151
prowe@crc.ac.uk

David Schlessinger
Department of Molecular Microbiology and
Center for Genetics in Medicine
Washington University School of Medicine,
Box 8230
660 S. Euclid Ave.
St. Louis, MO 63110
USA
Tel: 1-314-362-2744
Fax: 1-314-362-3203
davids@sequencer.wustl.edu

Charles Schwartz
JC Self Research Institute of Human Genetics
Greenwood Genetic Centre
One Gregor Mendel Circle
Greenwood SC 29646
USA
Tel: 1-803-941-8140
Fax: 1-803-941-8133
cschwrt@clust1.clemson.edu

Tim Strom
Abteilung Paediatrische Genetik
Ludwig-Maximilians-Universität
Goethestraße 29
D-80336 Munchen
GERMANY
Tel: 49 89 5160 4466
Fax: 49 89 5160 4780
tim@pedgen.med.uni-muenchen.de

R.V. Thakker
MRC Molecular Medicine Group
Royal Postgraduate Medical School
Hammersmith Hospital
DuCane Road
London W12 0NN
UK
Tel: 44-81-740-3014
Fax: 44-81-749-8341
rthakker@rpms.ac.uk

Daniela Toniolo
Istituto di Genetica Biochimica
e Evoluzionistica CNR
Via Abbiategrasso 207
27100 Pavia
ITALY
Tel: 39-382-546-340
Fax: 39-382-422-286
toniolo@ipvgbe.igbe.pv.cnr.it

Dorothy Trump
Royal Postgraduate Medical School
Hammersmith Hospital
DuCane Rd.
London W12 0NN
UK
Tel: 44 181 740 3014
Fax: 44 181 749 8341
dtrumpa@hgmp.mrc.ac.uk

Esther Van de Vosse
Department of Human Genetics
Leiden University
Wassenaarseweg 72
2333 AL Leiden
THE NETHERLANDS
Tel: 31-71-276105
Fax: 31-71-276075
esther@ruly46.MedFac.LeidenUniv.nl

David Vetrie
Paediatric Research Unit
Division of Medical and Molecular Genetics
7th Floor, Guy's Tower
London Bridge SE1 9RT
UK
Tel: 44-0171-955-2510
Fax: 44-0171-955-4644
d.vetrie@umds.ac.uk

Paolo Vezzoni
Istituto di Tecnologie Biomediche Avanzate - CNR
Via Ampère 56
20131 Milano
ITALY
Tel: 39-2-70643380
Fax: 39-2-2663030
frattini@itba.mi.cnr.it

Matthew Wakefield
School of Genetics and Human Variation
La Trobe University
Bundoora, Vic 3083
AUSTRALIA
Tel: 1-613-9479-2770
Fax: 1-613-9479-2480
genmjw@genome.zoo.latrobe.edu.au

Susan Wallace
HUGO Americas, Inc
7986 D Old Georgetown Road
Bethesda MD 20814
USA
Tel: 1-301-654-1477
Fax: 1-301-652-3368
hugo@gdb.org

Manfred Wehnert
Ernst-Moritz-Arndt University
Fleischmannstrasse 42/44
D-17489 Greifswald
GERMANY
Tel: 49-3834-88-2159
Fax: 49-3834-88-3355
wehnert@human1.rz.uni-greifswald.de

Huntington F. Willard
Department of Genetics
Case Western Reserve University
School of Medicine
2109 Adelbert Rd.
Cleveland OH 44106
USA
Tel: 1-216-368-1617
Fax: 1-216-368-3030
hfw@po.cwru.edu

John R.W. Yates
Department of Clinical Genetics
Box 134
Addenbrooke's Hospital NHS Trust
Cambridge CB2 2QQ
UK
Tel: 44 223 216446
Fax: 44 223 217054
jyates@hgmp.mrc.ac.uk

Andrew Zinn
The University of Texas Southwestern
Medical School
5323 Harry Hines Blvd.
Dallas, Texas 75235-8591
USA
Tel: 1-214-648-1615
Fax: 1-214-648-1666
andrew@mcdermott.swmed.edu

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Abstract titles of the sixth international workshop on human X chromosome mapping 1995

The complete abstract can be found in the GDB (GDB ID number).

A1

R. Nagaraja, S. MacMillan, J. Miao, C. Jones, B. Cho, B. Eble, G. Halley, M. Masisi, J. Terrell, M. Trusgnich, K. Wein, M. Shomaker, M. Blanchard, S. Kesterson, B. Railey, T. Featherstone, V. Nowotny, D. States, B. Brownstein and D. Schlessinger

Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA

STS/YAC-based integrated physical and genetic map of the human X chromosome (G00-581-825)

A2

M. Ross,[1] H. Roest Crollius,[2] C. Knights,[1] A. Grigoriev,[2] E. Holloway,[1] J. Mifsud,[1] K. Li,[1] R. Mott,[1] T. Labella,[1] H. Hummerich,[1] S. Gregory,[3] S. Humphray,[3] M. Playford,[1] R. Vatcheva,[1] C.G. See,[4] S. Marsh,[3] J. Kumlien,[1] K. Todd,[2] K. Rak,[2] T. Monaco,[5] D. Bentley,[3] G. Zehetner[2] and H. Lehrach[1,2]

[1] Genome Analysis lab, ICRF, London, UK, [2] Max-Planck-Institut fuer Molekulare Genetik, Berlin, Germany, [3] The Sanger Centre, Hinxton, UK, [4] UCL, London, UK, [5] Human Genetics Lab, ICRF, Oxford, UK

Whole X chromosome integrated mapping (G00-581-826)

A3

B. Korn,[1], S. Klauck,[1] G. Geiger,[1] H. Roest-Crollius,[2] H. Lehrach[2] and A. Poustka[1]

[1]Deutsches Krebsforschungszentrum, Abteilung fur Molekulare Genomanalyse, Heidelberg, Germany; [2]Max-Planck-Institut fur Molekulare Genetik, Berlin-Dahlem, Germany

An approach towards an X chromosome transcript map: combination of CpG cloning and cDNA selection (G00-581-827)

A4

M.S. Wehnert,[1] O. Zhuchenko,[2] I. Shumakov,[3] P. Rigault,[3] C.A. Chinault,[2] A. Baldini,[2] and C.C. Lee[2]

[1]Institute for Human Genetics, Ernst-Moritz-Arndt University Greifswald, Greifswald, Germany; [2]Baylor College of Medicine, Human Genome Center, Houston TX, USA; [3]CEPH, Foundation Jean Dausset, Paris, France

High resolution mapping of X-chromosomal cDNAS isolation by "reciprocal probing" (G00-581-828)

A5

B. Andersson, M. Wentland, D. Muzny, J. Lu, K. Timms, D. Nelson, and R. Gibbs

Department of Molecular and Human Genetics, Human Genome Center, Baylor College of Medicine, Houston TX

Strategies for megabase sequencing of regions of the human X-chromosome (G00-581-829)

A6

H. Lehrach

Max Planck Institut fur Molekulare Genetik, Dahlem, Berlin, Germany

Strategies in a global analysis of the human X chromosome (G00-581-830)

A7

F. Gianfrancesco,[1] T. Esposito,[2] L. Ruini,[3] M. D'Esposito,[1] C. Auffray,[2] R.Houlgatte,[2] M. D'Urso,[1] and A. Forabosco[3]

[1]International Institute of Genetics and Biophysics, CNR, Naples, Italy; [2]Centre National de la Recherche Scientifique, Villejuif, France; Sezione di Istologia Embriologia e Genetica, Dipartimento di Scienze Morfologiche e Medico Legali, Universite di Modena, Italy

Physical localization of 60 ESTs on the human X chromosome (G00-592-770)

A8

J. Kumlien,[1] A. Grigoriev,[1] H. Roest-Crollius,[1] M. Ross,[1] P. Goodfellow[2] and H. Lehrach[1]

[1]Department of Genome Analysis, Imperial Cancer Research Fund, London, UK, [2]Department of Genetics, University of Cambridge, Cambridge, UK

An integrated map spanning the entire human X chromsome using radiation fusion hybrids, YACS, genes and STS markers (G00-592-771)

B1

G.B. Ferrero,[1] B. Franco,[5] E.J. Roth,[2] B.A. Firulli,[1] G. Borsani,[5] J. Delmas-Mata,[5] J. Weissenbach,[3] D. Schlessinger,[4] A.C. Chinault,[1] H.Y. Zoghbi,[1,2] D.L. Nelson,[1] and A. Ballabio[5]

[1]Human Genome Center and Department of Molecular and Human Genetics; [2]Department of Pediatrics, Baylor College of Medicine, Houston TX; [3]Généthon, Evry, France; [4]Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO; [5]Telethon Institute of Genetics and Medicine, Milan, Italy

An integrated physical and genetic map of a 35-Mb region on chromosome Xp22.3-Xp21.3 (G00-581-772)

B2

D. Trump,[1] G. Pilia,[2] P.H. Dixon,[1] C. Wooding,[1] R. Thakrar,[1] S.E.A. Leigh,[1] R. Nagaraja,[2] M.P. Whyte,[3] D. Schlessinger,[2] and R.V. Thakker[1]

[1]MRC Molecular Endocrinology Group, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK; [2]Department for Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St Louis MO, USA; [3]Metabolic Research Unit, Shriners Hospital for Crippled Children and Washington University School of Medicine, St Louis MO USA

Construction of a YAC contig and an STS map spanning 3.6 megabase pairs in Xp22.1 (G00-581-773)

B3

Y. Gu,[1] G.B. Ferrero,[1] T. Schofield,[1] B.Franco,[2] C.C. Lee,[1] M. Graves,[1] A. Arenson,[1] A. Ballabio,[2] A.C. Chinault,[1] and D.L. Nelson[1]

[1]Human Genome Center and Departments of Molecular and Human Genetics and Cell Biology, Baylor College of Medicine, Houston TX, USA; [2]Telethon Institute of Genetics and Medicine, Milan, Italy

Towards a cosmid-based map of the distal short arm of the human X chromosome (G00-581-774)

B4

N.D.L. George,[1,4] S.J. Payne,[2] R.M. Bill,[2] D.E. Barton,[2] A.T. Moore[1] and J.R.W. Yates[3,4]

[1]Department of Ophthalmology; [2]Molecular Genetics Laboratory; [3]Department of Clinical Genetics, Addenbrooke's Hospital NHS Trust, Cambridge England; [4]Department of Pathology, University of Cambridge UK

Improved genetic mapping of X-linked retinoschisis (G00-581-775)

B5

E. Trivier,[1] C. Oudet,[1] S. Pannetier,[1] F. Francis,[2] P.S.N. Rowe,[3] and A. Hanauer[1]

[1]LGME/CNRS, U184/INSERM, Faculte de Medecine, Strasbourg, France; [2]Max-Planck-Institut fur Molekulare Genetik, Berlin, Germany; [3]University College London, Middlesex Hospital, London, UK

Construction of a functional map in the Xp22 region containing the Coffin-Lowry Syndrome (G00-581-776)

B6

E. Van De Vosse,[1] M.J.R. Van Der Wielen,[1] E.J. Meershoek,[1] A.A.B. Bergen,[4] J.C. Oosterwijk,[3] S. Gregory,[2] B. Bakker,[1] J. Weissenbach,[5] A.J. Coffey,[2] G.-J.B. Van Ommen,[1] and J.T. Den Dunnen[1]

[1]MGC-Department of Human Genetics, Leiden University, Leiden, The Netherlands; [2]The Sanger Centre, Hinxton Hall, Hinxton, Cambridge UK; [3]Clinical Genetics Centre Leiden, Leiden, The Netherlands; [4]The Netherlands Ophthalmic Research Institute, Amsterdam, The Netherlands; [5]Généthon, Evry, France

A 4-Mb Xp22.1→p22.2 YAC contig encompassing the disease loci for RS, KFSD, CLS and HYP; refined localization of RS and KFSD (G00-581-777)

B7

H. Bird, N.J. Goddard, O. O'Brien and S. Lindsay

Molecular Genetics Unit, Department of Human Genetics, University of Newcastle upon Tyne, UK

Further characterisation of the Coffin-Lowry Syndrome (CLS) gene candidate region in Xp22.13 (G00-581-778)

B8

F. Francis,[1] P.S.N. Rowe,[2] M.J. Econs,[3] C. Oudet,[4] T. Strom,[5] A. Hanauer,[4] S. Henni,[1] R. Reinhardt,[1] B. Korn,[6] A. Poustka,[6] P. de Jong,[7] T. Meitinger,[5] M.K. Drezner,[3] J.L.H. O'Riordan,[2] and H. Lehrach[1]

[1]Max-Planck-Institut für Molekulare Genetik, Berlin, Germany; [2]UCL Middx Hospital, London, UK; [3]Duke University, NC, USA; [4]IGBMC, Universite Louis Pasteur, Strasbourg, France; [5]Abteilung Paediatrische Genetik, München, Germany; [6]DKFZ, Heidelberg, Germany; [7]Roswell Park Cancer Institute, Buffalo NY, USA

Progress towards the transcriptional map and genomic sequence of the HYP gene candidate region (G00-581-779)

B9

P.S.N. Rowe,[1] J.N. Goulding,[1] F. Francis,[1] C. Oudet,[3] M.J. Econs,[4] A. Hanauer,[3] H. Lehrach,[2] A. Read,[5] R. Mountford,[5] T. Summerfield,[1] J. Weissenbach,[6] M.K. Drezner,[4] K.E. Davies,[7] and J.L.H. [1]O'Riordan

[1]University College London Middx Hospital, UK; [2]Max-Planck Institute, Germany; [3]CNRS/INSERM Universite Louis Pasteur France [4]Duke University NC, USA; [5]Manchester University UK; [6]Genethon France; [7]Oxford University UK

The HYP gene is localised to a single YAC containing a vitamin D response element, and is flanked by markers ~300 kb apart (G00-581-780)

B10

F. Muscatelli,[1] A.P. Walker,[1] E. De Plaen,[2] A.N. Stafford,[1] E. Burns,[1] and A.P. Monaco[1]

[1]ICRF Human Genetics Laboratory, Wellcome Trust Centre for Human Genetics, University of Oxford, Headington, Oxford UK; [2]Ludwig Institute for Cancer Research, Brussels Branch, Brussels, Belgiume

Isolation and characterisation of a new MAGE gene family in the Xp21.3 region (G00-581-781)

B11

A. Gal,[1] R. Kircheisen,[2] and B. Wittwer[3]

[1]Institut für Humangenetik, Universitäts–Krankenhaus Eppendorf, Hamburg; [2]Institut für Humangenetik der Universität Heidelberg; [3]Institut für Humangenetik der Universität, Münster, Germany

Gene of a new X-linked mental retardation syndrome maps in Xp22.2-pter (G00-581-782)

B12

A.P. Miller,[1,2] B. Eble,[3] J.R. Voland,[4] D. Schlessinger,[3] and H.F. Willard[1]

[1]Department of Genetics and Center for Human Genetics, Case Western Reserve University, Cleveland OH; [2]Department of Genetics, Stanford University, Stanford, CA; [3]Department of Molecular Microbiology, Washington University; School of Medicine, St. Louis MO; [4]Department of Biology, University of California, San Diego, La Jolla, CA USA

Localization of a lymphocyte surface antigen to the XP pseudoautosomal region (G00-581-783)

B13

B. Franco,[1] G. Meroni,[1] G. Parenti,[2] J. Levilliers,[3] L. Bernard,[1] M. Gebbia,[4] L. Cox,[1] P. Maroteaux,[5] L. Sheffield,[6] G.A. Rappold,[7] G. Andria,[2] C. Petit,[3] M.T. Bassi,[8] M.V. Schiaffino,[1] A. Renieri,[8] F. De Nigris,[1] L. Galli,[8] M. Bruttini,[8] A.A.B. Bergen,[9] R.A. Lewis,[4,10] and A. Ballabio[1]

[1]Telethon Institute of Genetics and Medicine (TIGEM), Milano, Italy; [2]Department of Pediatrics, University of Naples, Naples, Italy; [3]Unité de Génétique Moléculaire Humaine (CNRS UA 1445), Institut Pasteur, Paris, France; [4]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston TX, USA; [5]Hôpital des Enfants Malades, Paris, France; [6]The Murdoch Institute, Royal Children Hospital, Melbourne, Australia; [7]Institute für Humangenetik, Universität Heidelberg, Germany; [8]Department of Molecular Biology, University of Siena, Siena, Italy; [9]The Netherlands Ophthalmic Research Institute, Amsterdam The Netherlands; [10]Department of Ophthalmology, Baylor College of Medicine, Houston TX, USA

Cloning of the genes for X-linked recessive chondrodysplasia punctata (CDPX) and for ocular albinism Type I (OA1) from the Xp22 region (G00-581-784)

B14

A. Klink,[1] K. Schiebel,[1] M. Winkelmann,[1] E. Rao,[1] B. Horsthemke[2] and G.Rappold[1]

[1]Institut für Humangenetik, Universität Heidelberg, Germany; [2]Institut für Humangenetik, Universität Essen, Germany

The human protein kinase gene PKX on Xp22.3 Displays XP/YP homology and is a site of chromosomal instability (G00-581-785)

B15

K. Ried,[1] A. Mertz,[1] R. Nagaraja,[2] M. Trusnich,[2] J.H. Riley,[3] R. Anand,[3] H. Lehrach,[4] J. Ellison[5] and G. Rappold[1]

[1]Institut für Humangenetik, Universität Heidelberg, Heidelberg, Germany; [2]Center for Genetics in Medicine,Washington University St. Louis MO, USA; [3]Zeneca, Mereside Alderley Park, Maclesfield, UK; [4]MPI of Molecular Genetics, Berlin, Germany; [5]Department of Pediatrics, University of California, San Francisco CA, USA

Characterisation of a YAC contig spanning the pseudoautosomal region (G00-581-786)

C1

L. Colleaux,[1] M. May,[2] J. Belougne,[1] A. Aylsworth,[3] R. Nussbaum,[4] D. LePaslier,[5] M. Fontes,[1] and C. Schwartz[2]

[1]INSERM U406, Marseille, France; [2]Greenwood Genetic Center, Greenwood SC, USA; [3] Dept of Pediatrics, Chapel Hill, NC, USA; [4] NCHGR, Bethesda MD, USA; [5] CEPH, Paris, France

Construction of a 3.2-MB YAC contig encompassing a mental retardation gene in Xq21.1 (G00-581-800)

C2

S.M. van der Maarel,[1] C. Philippe,[2] H. van Bokhoven,[1] Y.J.M. de Kok,[1] I.H.J.M. Scholten,[1] C. Arnould,[3] F. Sloan,[3] J.T. den Dunnen,[4] G.J.B. van Ommen,[4] S.D. van der Velde-Visser,[1] M. Chery,[3] S. Gilgenkrantz,[3] H.H. Ropers,[1] A.P. Monaco,[2] F.P.M. Cremers[1]

[1]Department of Human Genetics, University Hospital Nijmegen, Nijmegen, The Netherlands; [2]The Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom; [3]Laboratoire de Genetique Humaine, Vandoevre-les-Nancy Cedex, France; [4]Department of Human Genetics, Silvius Laboratories, Leiden, The Netherlands

Detailed physical map of the Xq21 region by integrating deletions, X/autosome translocation breakpoints, and yeast artificial chromosome clones (G00-581-801)

C3

S. Mumm,[1] M. Shomaker,[1] J. Weissenbach,[2] and D. Schlessinger[1]

[1]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA; [2]Unite de Genetique Moleculaire Humaine, CNRS URA 1445, Institut Pasteur, Paris Cedex, France

YAC contigs in Xq21.1-q21.2 (G00-581-802)

C4

S. Mumm, B. Molini, J. Terrell and D. Schlessinger

Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis, MO USA

Physical map of the Xq21.3 X-Y homology region at 60 kb resolution (G00-581-803)

C5

Y.J.M. de Kok,[1] S.M. van der Maarel,[1] M. Bitner-Glindzicz,[2] I.J.H.M. Scholten,[1] I. Huber,[1] H.G. Brunner,[1] A.P. Monaco,[3] S. Malcolm,[2] E.M. Pembrey,[2] H.-H. Ropers,[1] F.P.M. Cremers[1]

[1]Department of Human Genetics, University Hospital Nijmegen, Nijmegen, The Netherlands; [2]Institute of Child Health, University of London, London, U.K.; [3]University of Oxford, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, U.K.

Cloning of the X-linked deafness gene (DFN3) by combining positional cloning and candidate gene approaches (G00-581-804)

C6

E. Kendall, W. Evans, H. Jin, M. Bobrow, and D. Vetrie

Paediatric Research Unit, Division of Medical and Molecular Genetics UMDS of Guy's and St. Thomas's Hospitals, Guy's Tower, London UK

Completion of a detailed YAC map covering the entirety of Xq21.33-Xq22 from DXS3 to DXS287 (G00-581-805)

C7

H. Steingruber,[1] A. Dunham,[1] A. Coffey,[1] S. Humphray,[1] G. Maslen,[1] C. Soderlund,[1] H. Lehrach,[2] M. Ross[1] and D. Bentley[1]

[1]The Sanger Centre, Hinxton Hall, Hinxton, Cambridge, UK; [2]Max-Planck-Institut fur Molekulare Genetik, Berlin, Germany

Towards a fully integrated map of the Xq23-q25 region (G00-581-806)

C8

A.J. Coffey,[1] A. Dunham,[1] G.R. Howell,[1] S. Rhodes,[1] R. Brooksbank,[1] S. Marsh,[1] H. Steingruber,[1] A. Harris,[2] G. Porta,[3] D. Schlessinger,[4] and D.R. Bentley[1]

[1]Sanger Centre, Hinxton Hall, Hinxton, Cambridge, UK; [2]Institute of Molecular Medicine, Oxford University, Oxford, UK; [3]University of Pavia, Department of Human Genetics, Pavia, Italy; [4]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA

Construction of a 2-3 MB YAC contig in Xq25 in the critical region for XLP and reordering of the consensus map (G00-581-807)

C9

G. Porta,[1,2] S. MacMillan,[3] R. Nagaraja,[3] J. Miao,[3] S. Mumm,[3] S. Sirchia,[1] A. Coffey,[4] D.R. Bentley[4] and D. Schlessinger[3]

[1]Instituto di Scienze Biomediche San Paolo, Universita di Milano; [2]Ereditaria Universita di Pavia Italy; [3]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA; [4]Sanger Centre, Hinxton Hall, Hinxton, Cambridge, England UK

YAC/STS contig of 4 Mb across two deletions spanning the LYP locus in Xq25

C10

R. Nagaraja,[1] S. MacMillan,[1] J. Miao,[1] G. Pilia,[1] I. Zucchi,[1] G. Porta,[1] M. Masisi,[1] A. Jauch,[2] T. Featherstone,[1] J. Weissenbach[3] and D. Schlessinger[1]

[1]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA; [2]Institut fur Humangenetik, Heidelberg, Germany; [3]Unite de Genetique Moleculaire Humaine, CNRS URA 1445, Insitut Pasteur, Paris Cedex, France

Progress towards YAC/STS content mapping of Xq24-q26.1 (G00-581-809)

C11

R. Nagaraja,[1] C.-N. Chen,[2] Y. Su,[2] P. Baybayan,[2] R. Mazzarella,[1] D. Schlessinger,[1] and E.Y. Chen[2]

[1]Department of Molecular Microbiology, Washington University School of Medicine, St. Louis MO; [2]Advanced Center for Genetic Technology, Applied Biosystems Division of Perkin Elmer Corp., Foster City CA, USA

Sequencing a 140-kb human YAC clone by ordered shotgun sequencing (OSS) strategy (G00-581-810)

C12

A. Srivastava,[1] T. Featherstone,[1] M. Shomaker,[1] J. Weissenbach[2] and D. Schlessinger[1]

[1]Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO, USA; [2]Unite de Genetique Moleculaire Humaine, CNRS URA 1445, Insitut Pasteur, Paris Cedex, France

YAC/STS contigs between the X-Y homology region in Xq21.3 and Xq24 (G00-581-811)

C13

C. Sala,[1] F. Martinazzi,[1] G. Torri,[1] P. Riva,[3] L. Larizza[3] and D. Toniolo[2]

[1]DIBIT-HSR, Milano, [2]Istituto di Genetica Biochimica ed Evoluzionistica, CNR, Pavia; [3]Dipartimento di Biologia Generale, Universit` di Milano, Italy

Physical map of the critical region for premature ovarian failure in Xq21 and mapping of balanced translocation breakpoints (G00-592-768)

I1

C.J. Porter and A.J. Cuticchia

Genome Data Base, The Johns Hopkins University School of Medicine, Baltimore MD USA

The role of the Genome Data Base at the X chromosome workshop (G00-626-046)

I2

R.W. Cottingham

Human Genome Center and the Department of Molecular and Human Genetics Baylor College of Medicine, Houston TX, USA

X Chromosome Virtual Workshop-a network service (G00-581-838)

M1

J. Chai, Y. Wei, X. Wu, W. Miao, H. Ma, Y. Xu, X. Wu, Y. Kang and W. Deng

Human Genome Laboratory, Institute of Genetics, Fudan University, Shanghai, China

YAC-based mapping and cDNA mapping of human X chromosome Xp11.1-p21.3 spanning 35 cM (G00-581-787)

M2

J.M.J. Derry, J.A. Kems, U. Jess and U. Francke

Howard Hughes Medical Institute, Beckman Center for Molecular and Genetic Medicine, Stanford University, Stanford CA, USA

A YAC and transcript map of the Xp11.23 region surrounding the Wiskott-Aldrich Syndrome (G00-581-788)

M3

A.R. Zinn,[1] S. Garcia,[1] B. Ouyang,[1] and J.L. Ross[2]

[1]Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas TX; [2]Department of Pediatrics, Thomas Jefferson University Medical School, Philadelphia PA, USA

Mapping Turner Syndrome loci on the X Chromosome (G00-581-789)

M4

A.J. Hardcastle,[1] R.M. Hampson,[1,3] D.L. Thiselton,[1] M. Nayudu,[1] A. Meindl,[2] S.E. Jones,[3] and S.S. Bhattacharya[1]

[1]Department of Molecular Genetics, Institute of Ophthalmology London, UK; [2]Abteilung Padiattrische Genetik der Kinderpoliklinik, Munich Germany.; [3]Rayne Institute, St Thomas' Hospital, London, UK

Genetic and physical mapping of the RP2 critical region (G00-581-790)

M5

A. Villa,[1] G. Notarangelo,[2] P. Macchi,[1] D. Strina,[1] S. Giliani,[2] E. Mantuano,[2] A. Ugazio[2] and P.Vezzoni[1]

[1]Institute of Advanced Biomedical Technologies (ITBA), National Research Council (CNR), Milan, and [2]Department of Pediatrics, University of Brescia, Brescia, Italy

Mutations of the WASP Gene in X-Linked Thrombocytopenia (G00-581-791)

M6

R. Nagaraja, M. Trusgnich, A. Srivastava and D. Schlessinger

Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA

Integrated YAC/STS Map of the DMD region (G00-581-792)

M7

A. Chand,[1] S.E. Fisher,[1] E. Hatchwell,[1] N. Ockendon,[1] J. Clark,[2] C.S. Cooper,[2] A. Monaco,[3] and I. Craig[1]

[1]Genetics Laboratory, Department of Biochemistry, Oxford, UK; [2]Institute of Cancer Research, Haddow Laboratories, Sutton, Surrey, UK; [3]Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK

YAC contigs, physical mapping of Xp11.23-p11.22 and detailed analysis of the OATL1 locus (G00-581-793)

M8

A. Meindl,[1] M.R.S. de Carvalho,[1] D. Schindelhauer,[1] K. Herrmann,[1] L. Grimm,[1] M. Wehnert,[2] M.T. Ross,[3] and T. Meitinger[1]

[1]Abteilung Paediatrische Genetik der Kinderpoliklinik, Muenchen; [2]Institut fur Humangenetik, Greifswald, Germany; [3]ICRF, Genome Analysis Laboratory, London, UK

Two novel genes mapped to cosmid contigs in Xp21.1 and Xp11.23 (G00-581-794)

M9

K.M. Boycott,[1] G. Halley,[2] D. Schlessinger,[2] and N.T. Bech-Hansen[1]

[1]Department of Paediatrics, University of Calgary, Calgary, Alberta, Canada; [2]Human Genome Center, University of Washington, St. Louis MO, USA

Development of a physical contig of the human X chromosome at Xp11.23-p11.22 and isolation of coding sequences by direct selection (G00-592-767)

N1
G. Haberhausen,[1] I. Schmitt,[1] U. Peters,[1] A. Köhler,[1] N. Brockdorff,[2] M. Fontes,[3] A.P. Monaco,[4] and U. Müller[1]
[1]Institut für Humangenetik der Justus-Liebig-Universität; Giessen, Germany; [2]Section of Comparative Biology, MRC Clinical Research Centre, Harrow, UK; [3]INSERM U406, Marseille, France; [4]Wellcome Trust Centre for Human Genetics, University of Oxford, Headington, Oxford, UK
Delineation of DYT3 within a small region of an 1.8-MB YAC - contig in Xq13.1 and characterization of two candidate genes of the X-linked Dystonia Parkinsonism Syndrome (XDP) (G00-581-795)

N2
L. Villard, L. Colleaux, A.M. Lossi, J. Belougne, M. Fontés
INSERM U406, Faculté de Médecine de la Timone, Marseille Cedex, France
Physical and transcriptional mapping in Xcen-q21.3: association with inherited diseases (G00-581-796)

N3
L. Villard,[1] A. Toutain,[2] C. Moraine,[2] and M. Fontés[1]
[1]INSERM U406, Faculté de Médecine de la Timone, Marseille Cedex, France; [2]Centre de Génétique Médicale, Hospital Bretonneau, Tours, France
XNP, A gene coding for a potential global transcriptional factor, is involved in the ATRX and related MR syndromes (G00-581-797)

N4
U. Orth,[1] H–L. Riggert,[2] E. Schwinger,[1] and A. Gal[3]
[1]Institut für Humangenetik, Medizinische Universität, Lübeck, [2]Kinderabteilung, Städtisches Krankenhaus, Salzgitter, and [3]Institut für Humangenetik, Universitüts–Krankenhaus Eppendorf, Hamburg, Germany
Gene for X-linked form of congenital failure of autonomic control of ventilation maps between DXS7 and DXS441 (G00-581-798)

N5
A.P. Miller,[1,2] M.K. Graves,[1] A.P. Monaco,[3] B. Eble,[4] D. Schlessinger,[4] and H.F. Willard[1]
[1]Department of Genetics, Case Western Reserve University, Cleveland, OH, USA; [2]Department of Genetics, Stanford University, Stanford, CA, USA; [3]Imperial Cancer Research Fund, University of Oxford, Oxford, UK; [4] Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO, USA
Progress in mapping the pericentromeric region of the human X chromosome: YAC contigs spanning Xp11.21-p11.22 and Xq11.2-q12 (G00-581-799)

P1
N. Quaderi, A. Haynes, G. Argyropoulos, P. Mileham and S.D.M. Brown
Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London, UK
An anchored YAC framework map of the mouse X chromosome (G00-581-831)

P2
Y. Boyd, H.J. Blair, I.C. Uwechue, E. Gormally and S.H. Laval
MRC Radiobiology Unit, Chilton Didcot, Oxfordshire, UK
Xp21.1-Xpcen: genetic and physical mapping of the equivalent regions on the mouse X chromosome (G00-581-832)

P3
G. Herman,[1] A. Chatterjee,[1] B. de Gouyon,[1] M. Levin,[1] N. Quaderi,[2] and S.D.B. Brown[2]
[1]Department of Molecular and Human Genetics, Baylor College of Medicine USA; [2]Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, London UK
Comparative physical mapping of the mouse X chromosome between IDS and DMD and Human Xq28 (G00-581-833)

P4
G. Nyakatura,[1] O. Coutelle,[1,2] G. Elgar,[2] S. Brenner,[2] M. Platzer,[1] B. Drescher[1] and A. Rosenthal[1]
[1]Institute of Molecular Biotechnology, Department of Genome Analysis, Jena, Germany; [2]Department of Medicine, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, UK
Comparative sequencing in human and the pufferfish FUGU: the locus for the neural cell adhesion molecule L1 (G00-581-834)

P5
D.W. Cooper,[1] P.G. Johnston,[1] R.L. Hughes,[2] R. Gemmell,[2] M. Smith[3] and C.M. Watson[1]
[1]School of Biological Sciences, Macquarie University; [2]Department of Anatomy, University of Queensland, [3]Evolutionary Biology Unit, South Australian Museum, North Terrace, Adelaide, SA
X-chromosome involvement in marsupial sex differentiation (G00-581-835)

P6
M.J. Wakefield and J.A. Marshall Graves
School of Genetics and Human Variation, La Trobe University, Bundoora, Victoria, Australia
A comparative map of the X chromosome (G00-581-836)

P7
E.I. Rugarli,[1] D.A. Adler,[2] G. Borsani,[1] K. Tsuchiya,[2] B. Franco,[1] C. Disteche,[2] V. Chapman,[3] and A. Ballabio[1,4]
[1]Telethon Institute of Genetics and Medicine, Milano, Italy; [2]University of Washington, Seattle WA; [3]Roswell Park Cancer Institute, Buffalo NY, USA; [4] University of Siena, Siena, Italy
Different map assignment of the *Clcn4* gene in *Mus Spretus* and *Mus Domesticus* provides evidence for genetic divergence underlying Haldane's Rule (G00-581-837)

S1
P.H. Dixon,[1] D. Trump,[1] M.P. Whyte,[2] S. Mumm,[3] D. Schlessinger[3] and R.V. Thakker[1]
[1]MRC Molecular Endocrinology Group, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK; [2]Metabolic Research Unit, Shriners Hospital for Crippled Children and Washington University School of Medicine, St Louis MO USA; [3]Department for Molecular Microbiology and Centre for Genetics in Medicine, Washington University School of Medicine, St Louis MO USA
Linkage analysis of six polymorphic loci (DXS1001, DXS102, DXS984, DXS1232, DXS1205, DXS1227) in X-linked recessive hypoparathyroid families (G00-581-812)

S2

S. Joseph,[1] Y. Shiloh[2] and D. Bentley[1]

[1]The Sanger Centre, Hinxton Hall, Hinxton, Cambridgeshire, UK; [2]Department of Human Genetics, Sackler School of Medicine, Tel-Aviv University, Ramat Aviv, Israel

Refinement of the X-linked albinism-deafness (ADFN) localisation by genetic mapping in a Jewish kindred (G00-581-813)

S3

I. Zucchi,[1,2] S. Mumm,[1] G. Pilia,[1] S. MacMillan,[1] R. Reinbold,[1] L. Susani,[2] J. Weissenbach[3] and D. Schlessinger[1]

[1]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO USA; [2]C.N.R.-I.T.B.A. Milano, Italy; [3]Unite de Genetique Moleculaire Humaine, CNRS URA 1445, Insitut Pasteur, Paris Cedex, France

YAC-based contig formatted across 12 Mb and 24 cM of Xq27 (G00-581-814)

S4

J. Gecz,[1] A.K. Gedeon,[1] H. Kaariainen,[2] G.R. Sutherland,[1] and J.C. Mulley[1]

[1]Department of Cytogenetics and Molecular Genetics, Centre for Medical Genetics, Women's and Children's Hospital, North Adelaide, Australia; [2]Department of Medical Genetics, University of Helsinki, Helsinki, Finland

Cloning of a candidate gene(s) interrupted by overlapping submicroscopical deletions near FRAXE in two boys with developmental delay (G00-581-815)

S5

A. Poustka, U.C. Rogner and K. Wilke

Deutsches Krebsforschungszentrum, Abteilung für Molekulare Genomanalyse, Heidelberg, Germany

MAGE genes are clustered in three main intervals in human Xq28 (G00-581-186)

S6

J.E. Parrish, E.E. Eichler, Y. Gu, B. A. Firulli, C.C. Lee, M. Graves, A. Arenson, T. Schofield, and D.L. Nelson

Department of Molecular and Human Genetics, Human Genome Center, Baylor College of Medicine, Houston TX, USA

Cosmid contig construction and gene identification in Xq28 (G00-581-817)

S7

M. Platzer,[1] D. Bauer,[1] V. Brenner,[1] O. Coutelle,[1] B. Drescher,[1] G. Nyakatura,[1] K. Reichwald,[1] N. Sandoval,[1] P. Kioschis,[2] J.F. Coy,[2] B. Korn,[2] A.M. Poustka,[2] D. Bentley,[3] G. Senger,[4] A. Rosenthal[1]

[1]Institute of Molecular Biotechnology, Department of Genome Analysis, Jena, Germany; [2]Institute of Virus Research/ATV, German Cancer Research Centre, Heidelberg, Germany; [3]The Sanger Centre, Hinxton Hall, Hinxton, Cambridge UK; [4]Institute of Human Genetics and Anthropology, F. Schiller Univerisity, Jena, Germany

Sequencing and analysis of 360 kb of human Xq28 genomic DNA in the region of the L1CAM locus (G00-581-818)

S8

E.E. Eichler,[1] F. Lu,[1] R. Antonacci,[1] N. Doggett,[2] R. Moyzis,[2] A. Baldini,[1] C.C. Lee,[1] R.A. Gibbs,[1] and D.L. Nelson[1]

[1]Human Genome Center and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston TX; [2]Los Alamos National Laboratory, Los Alamos NM, USA

A gene-rich duplication between Xq28 and 16p11.1 suggests a novel mechanism for genome evolution (G00-581-819)

S9

M. D'Urso,[3] M. Zollo,[1] A. Arcucci,[1] M. Repetto,[1] C. Heiner,[1] C.N. Chen,[1,2] R. Mazzarella,[2] F. Burough,[2] D. Schlessinger,[2] C. Migliaccio,[3] M. Cocchia,[3] A. Ciccodicola[3] and E.Y. Chen[1]

[1]Advanced Center for Genetic Technology, Applied Biosystems Division of Perkin-Elmer Corp., Foster City, CA ; [2]Department of Molecular Microbiology, Washington University School of Medicine, St. Louis MO; [3]International Institute of Genetics and Biophysics, CNR, Naples, Italy

Sequence analysis of 220 kb of high GC DNA between the RCP/GCP and G6PD loci in human Xq28 (G00-581-820)

S10

E.Y. Chen,[1] R. Mazzarella,[2] F. Burough,[2] C.-N. Chen,[1] M. D'Esposito,[3] A. Ciccodicola,[3] M. D'Urso[3] and D. Schlessinger[2]

[1]Advanced Center for Genetic Technology, Applied Biosystems Division of Perkin Elmer Corp., Foster City CA; [2]Department of Molecular Microbiology and Center for Genetics in Medicine, Washington University School of Medicine, St. Louis MO, USA; [3]International Institute of Genetics and Biophysics, Naples, Italy

Gene predicitons and verification in 220 kb of human Xq28 between the RCP/GCP and G6PD loci (G00-581-821)

S11

T. Esposito,[1,2] L. Flagiello,[1] A. Ciccodicola,[1,2] C. Migliaccio,[1] M.R. Matarazzo,[1] F. Gianfrancesco,[1] M. D'Esposito[1] and M. D'Urso[1]

[1]International Institute of Genetics and Biophysics, CNR, Naples, Italy; [2]Department of Scienze Morfologiche and Medico-Legali, University of Modena, Italy

Transcriptional analysis of Xq28 region (G00-581-822)

S12

T. Brown, N. Zhong, D. Curley, W. Ju, D.W. Wang, C. Dobkin

Department of Human Genetics, Institute for Basic Research, Staten Island NY, USA

A general method for finding new polymorphisms: identification of an ALU SSCP polymorphism in the Fragile X gene (G00-581-823)

S13

T. Brown, N. Zhong, W. Wang, G.E. Houck, X. Ding, E. Jenkins, C. Dobkin

Department of Human Genetics, Institute for Basic Research, Staten Island NY, USA

Identification of a FRAXE microdeletion associated with a complex mosaic FRAXA mutation (G00-581-824)

S14

S. Bione,[1] E. Maestrini,[1] P. D'Adamo,[1] S. Rivella,[1] L. Tamagnone,[2] P. Comoglio,[2] S. Droetto,[3] P.G. Pelicci,[3] M. Gulisano,[4] F. Tamanini,[1] M. Mancini,[1] F. liBergolis,[1] C. Tribioli[1] and D. Toniolo[1]

[1]Istituto di Genetica Biochimica ed Evoluzionistica, CNR, Pavia; [2]Department of Medical Sciences, U. of Torino; [3]Department of Medicine, U. of Perugia; [4] DIBIT-HSR, Milano, Italy

New genes, disease genes and the transcriptional map of distal Xq28 (G00-592-769)